Pharma-Fun in Cardiovascular and Blood Pharmacology

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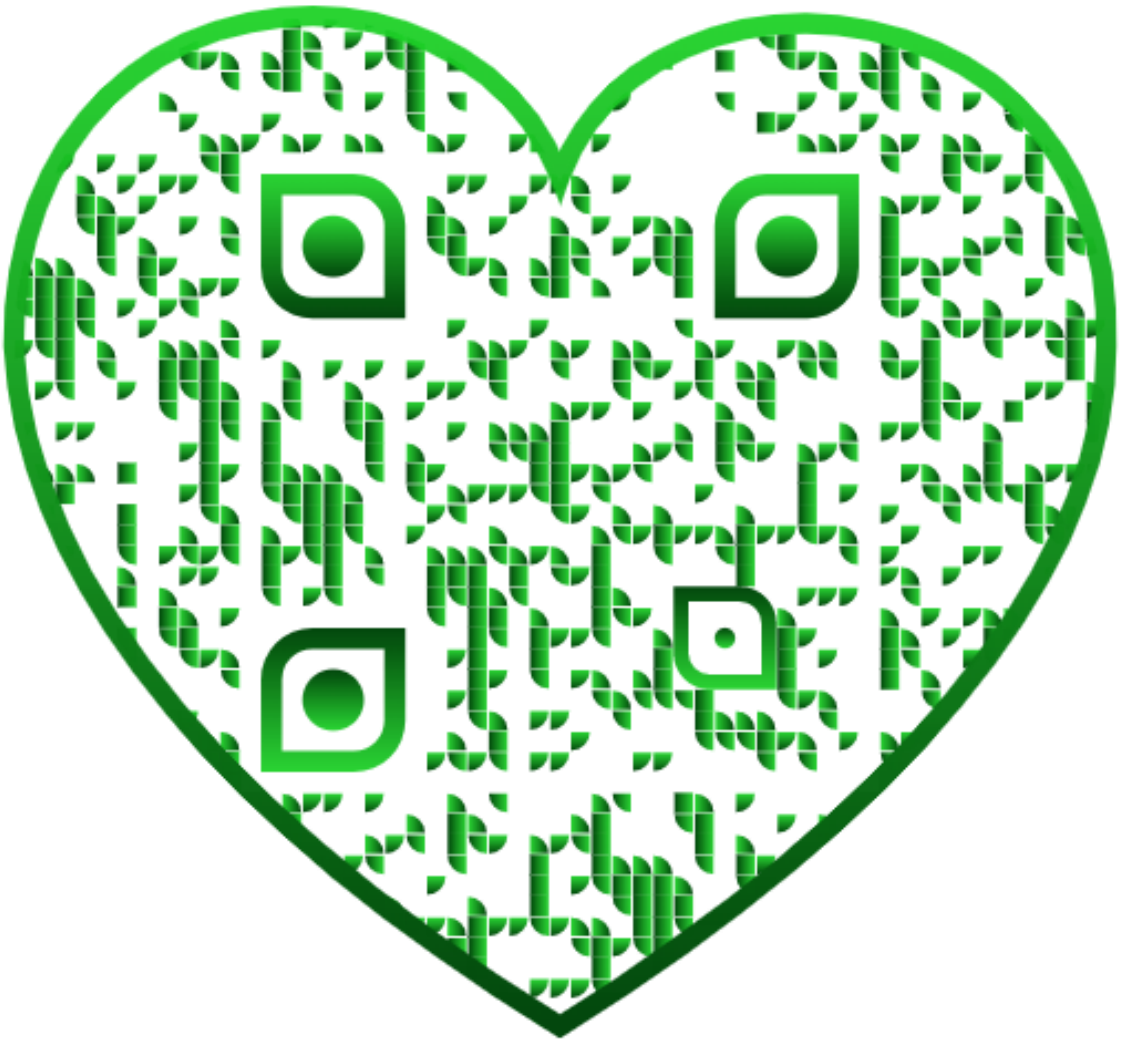

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Chapter 1

Drugs for Congestive Heart Failure (CHF)

Congestive Cardiac Failure (CCF)
= Congestive Heart Failure

Definition:

A clinical syndrome resulting from inadequacy of cardiac output to maintain perfusion of tissues in the body.

This leads to:

- ↓ exercise tolerance.
- ↑ heart rate.
- ↑ susceptibility to ventricular arrhythmias.
- Edemas.

Causes of CHF:

1) ↑ preload (load of blood volume arriving in the heart) due to:
   a) Heart valve diseases
   b) Renal failure

2) ↑ afterload (hypertension overload) due to:
   a) Arteriolar hypertension ➡ left-sided heart failure.
   b) Pulmonary hypertension ➡ right-sided heart failure.

3) Cardiac muscle disease due to:
   a) Myocardial infarction.
   b) Myocarditis.
   c) Cardiomyopathy.

* Preload = volume of blood reaching the heart before contraction
* Afterload = resistance of arterioles to blood pumped by the heart
* Increased preload or afterload to a certain level increase heart contraction force. But if they increased post a certain level, that may lead to heart failure.

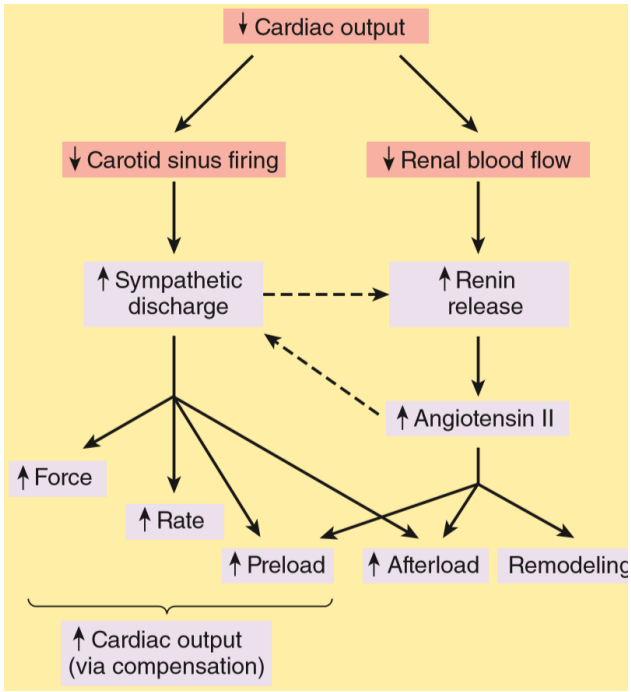
Symptoms:

1) Ischemic symptoms
   - brain ➝ confusion.
   - heart ➝ angina pectoris.
   - muscles ➝ fatigue & pain during exercise.
   - kidney ➝ renal failure.

2) Congestive symptoms (edemas)
   - General edemas starting from lower limbs then upwards.
   - GIT ➝ nausea & vomiting.
   - liver ➝ hepatic enlargement.
   - pulmonary congestion ➝ dyspnea & shortness of breath.

3) Compensatory mechanisms
   - ↑ heart rate.
   - ↑ RAAS → ↑ BP & cardiomegaly.

Compensatory mechanisms



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Notes:

* The disturbance of ventricular functions could be:

A) Systolic failure (main)

The ventricles are not strong enough to pump enough blood.

B) Diastolic failure (rigidity):

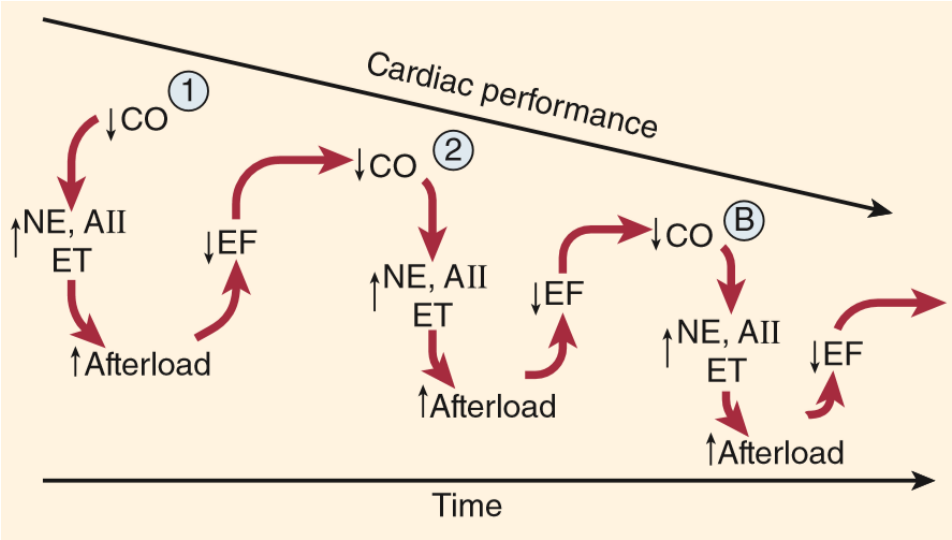
The ventricles do not relax enough to get enough blood.

* Sometimes CHF may occur as a result of increased cardiac work & exhaustion e.g. anemia, thrombosis, vasodilatation.

* C.H.F usually deteriorates and gets worse with time because:

↓ cardiac output ➞ ↓ kidney perfusion:

- → 1) ↑ blood volume. (↑ preload)
- → 2) ↑ renin secretion from kidney ➡ ↑ angiotensin II.
  - ⇨ vasoconstriction (↑ afterload)
  - ⇨ ↑ aldosterone ➞ ↑ water & salt retention (↑ preload)
  - ⇨ cardiac remodeling



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Degrees: (according to the New York Association)

Class 1

- ☞ slight limitations of excessive physical activity.
- ☞ no symptoms at rest

Class 2

- ☞ slight limitations of ordinary activities
  (shortness of breath, fatigue & palpitation)

Class 3

- ☞ limitation of less than ordinary activities.

Class 4

- ☞ severe limitation & other symptoms at rest (even sleep is hard)

Class 5

- ☞ cardiogenic shock (irreversible; ↓↓ BP & organs failure)
- ☞ fatal if not treated immediately

Purpose of drug therapy:

1) ↓ preload
   - Diuretics.
   - Venodilators.

2) ↓ afterload
   - Diuretics.
   - Arteriolar vasodilators.

3) ↓ cardiac work
   - β blockers.

4) ↑ cardiac output (+ve inotropic agents)
   - β1 agonists.
   - Phosphodiesterase inhibitors.
   - Ca sensitizers.
   - Cardiac glycosides.

Notes:
There are many approaches to treat CHF but one approach is:

- CHF class 1
  → vasodilators enough
- CHF class 2 & 3
  → vasodilators (ACEIs) + diuretics
- CHF class 4 & 5
  → vasodilators (ACEIs) + diuretics + positive inotropic agents

* Currently, a triple therapy is preferred in heart failure:
  → ACE inhibitor + β blocker + aldosterone antagonist.

* You need to know what the following “terms” mean:
  - Preload vs afterload - stroke volume vs cardiac output
  - Systolic vs diastolic CHF - Left-sided vs right-sided CHF

1) Diuretics

☺ **Role in treating CHF (purpose):**

1) ↓ blood volume ➡ ↓ preload & ↓ afterload.

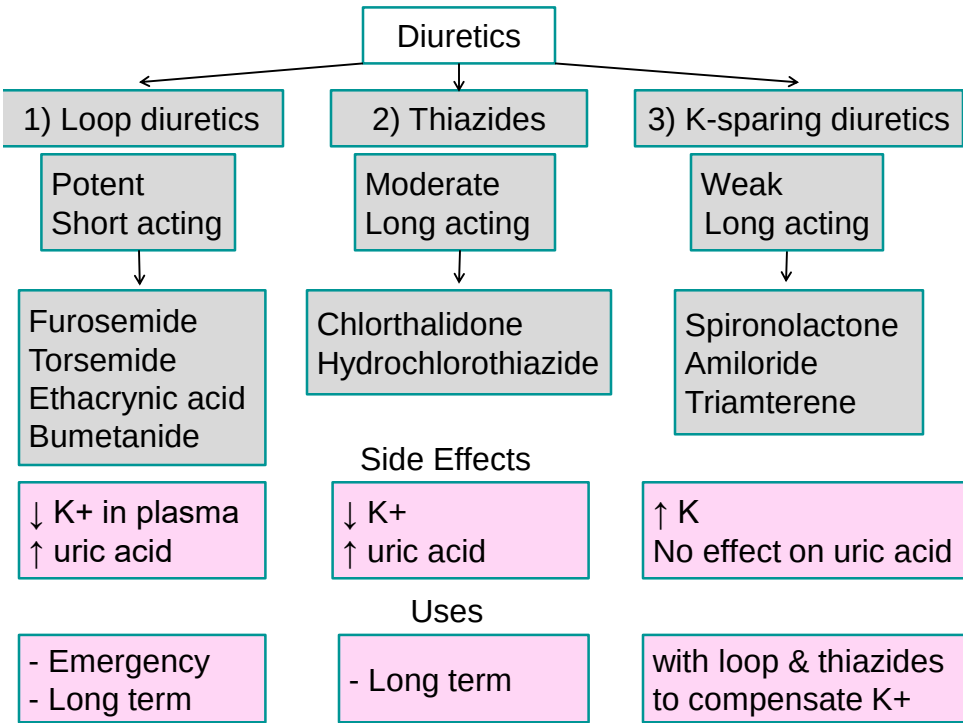
2) mild vasodilation: in veins ➡ ↓ preload
in arteries ➡ ↓ afterload.

3) diuresis ➡ ↓ congestive symptoms.

☹ **Disadvantages in treating CHF:**

1) ↓ blood volume ➡ ↑ ischemic symptoms.

2) most diuretics cause k loss ➡ ↑ arrhythmia



Diuretics used in CHF:

1) Loop diuretics

Called so because they work in the ascending loop of Henle of the nephron.

e.g. furosemide, torsemide, ethacrynic acid, bumetanide.

Characteristics:

* potent & short action.
* The only group effective in cases of severe renal impairment.
* May cause: ↓ k & ↑ uric acid in blood.

Use:

1) 1st choice for emergency cases of CHF.
2) Can also be used in long-term therapy.

* Ethacrynic acid is rarely used due to its high ototoxicity.

* Furosemide i.v. promptly mitigates dyspnea in acute left ventricular failure by increasing venous capacitance and reducing cardiac preload.

2) Thiazides

Include both thiazides and thiazide-like drugs.

Thiazides:

→ Cholorothiazide, hydrochlorothiazide, bendroflumethiazide, hydroflumethizide.

Thiazide-like drugs:

→ chlorthalidone, metolazone & indapamide “Natrilix®”

Characteristics:

1) Intermediate & long action.
2) May cause ↓ k & ↑ uric acid (worse than loop diuretics)
3) May cause ↑ Ca in plasma (→ fatigue & depression)

Use:

- Long-term therapy of CHF

3) Potassium-sparing diuretics

Include:

- Aldosterone receptor antagonist: spironolactone & eplerenone
- Na channel blockers: triameterine & amiloride.

Characteristics:

1) weak & slow action.
2) Do not affect k (or may increase) or uric acid.

Use:

With strong diuretics (loop or thiazides) to prevent K^+ loss.

Note:

↓ k+ in blood (hypokalemia) may lead to:

1) Muscle pain & weakness
2) Arrhythmias.
3) ↓ insulin secretion ➡ hyperglycemia & hyperlipidemia.

2) Vasodilators

☺ Role in CHF:

1) Vasodilation of veins → ↓ preload

2) Vasodilation of arteries → ↓ afterload

- ↓ preload & afterload → ↓ cardiac work, leading to:
  1) ↓ fibrosis
  2) ↓ release of lysosomal enzymes
  3) ↓ cardiomegaly.

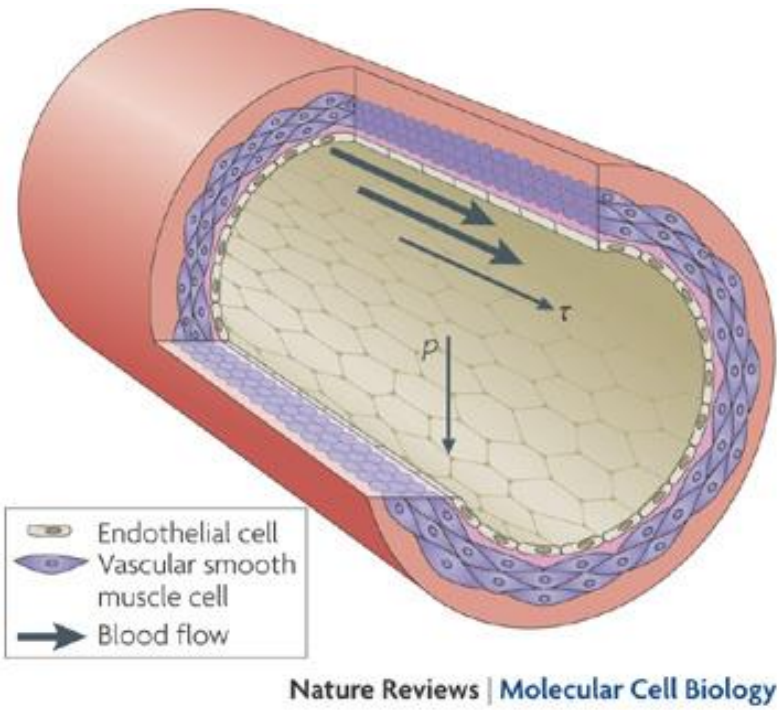
☹ Disadvantages:

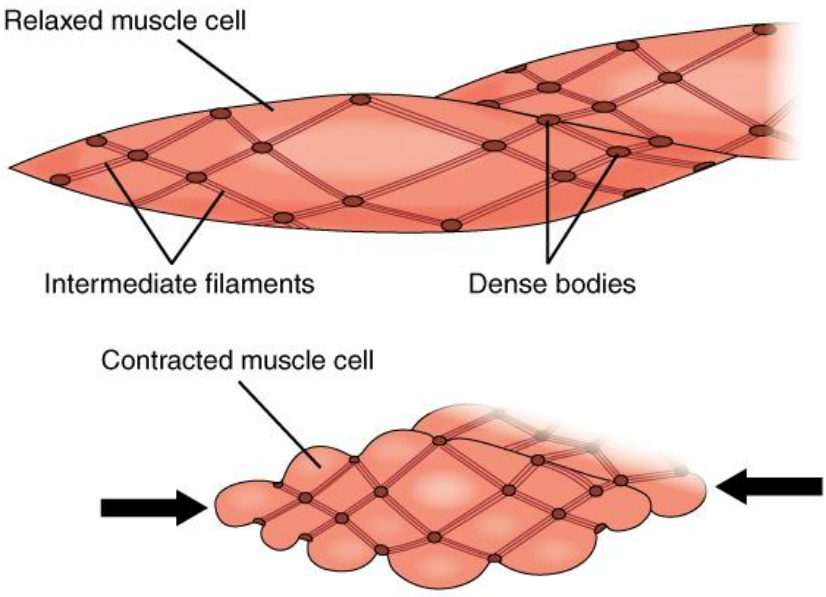
1) Reflex tachycardia may occur. (add a β blocker)

2) Hypotension & other side effect may occur.

Vasodilators

Dilate Arteries	Dilate veins	Dilate Arteries & veins
Hydralazine Minoxidil Diazoxide Fenoldopam	Nitrates	1) Na Nitroprusside 2) Ca channel blockers: - Nifidepine - Diltiazem - Verapamil 3) AT antagonists: - ACEIs (-prils) - ARBs (-sartans)





Smooth muscle cells (relaxed & contracted)

(https://en.wikipedia.org/wiki/Smooth_muscle_tissue)

MOAs of Vasodilators:

MOA	Drugs
1) ↑ Nitric oxide (NO) (from drug breakdown or from endothelium)	Nitrates, nitroprusside, hydralazine, (also H & Ach)
2) Opening K+ channels (in SMCs of blood vessels)	Minoxidil, diazoxide
3) Blocking Ca++ channels (in SMCs of blood vessels)	Nifedipine, amlodipine verapamil, diltiazem
4) ↑ D1 receptors (in SMCs of blood vessels)	Fenoldopam

SMCs = smooth muscle cells (in the walls of vessels)

* Ca channel blockers:

↓ Ca entry into vascular smooth muscle cells & cardiomyocytes.

☑ **Dihydropyridine group** (vasculo-selective)

Agents:

Short → Nifidipine

Long → Amlodipine (causes less tachycardia)

Others: nimodipine, nisodipine, nicardipine, felodipine, isradipine, clevidipine

Action:

Blocks non-functioning Ca channels (in blood vessels) > functioning Ca channels (in the heart)

⇨ leads to: vasodilatation (+++) + reflex tachycardia.

Use:

* Antihypertensive (+++). (nifedipine is also used as a tocolytic)

Side effects:

reflex tachycardia.

☑ Non-dihydropyridine group (cardio-selective)

Agents:

Verapamil (stronger cardio-depressant; preferred over diltiazem)

Diltiazem (weaker cardio-depressant)

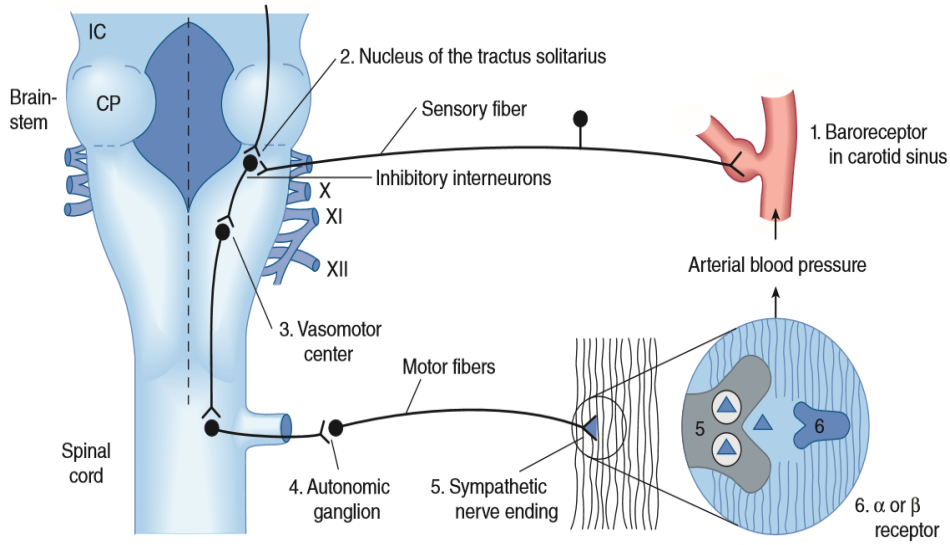
Action:

Blocks functioning Ca channels (in the heart) > non-functioning Ca channels (in blood vessels)

⇨ leads to significant cardio-depression with little vasodilatation.

Use:

* Antihypertensive. (+)
* Anti-angina. (+++)
* Anti-arrhythmic. (+++)
* Hypertrophic obstructive cardio-myopathy “HOCM” (+++)
* Have been used in the past for CHF but not anymore.



11–2 Baroreceptor reflex arc. IC, inferior colliculus; CP, cerebellar peduncle.

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Notes

* Dihydropyridines affect blood vessels > heart. (may cause reflex tachycardia) → so verapamil is preferred over nifedipine in heart diseases.

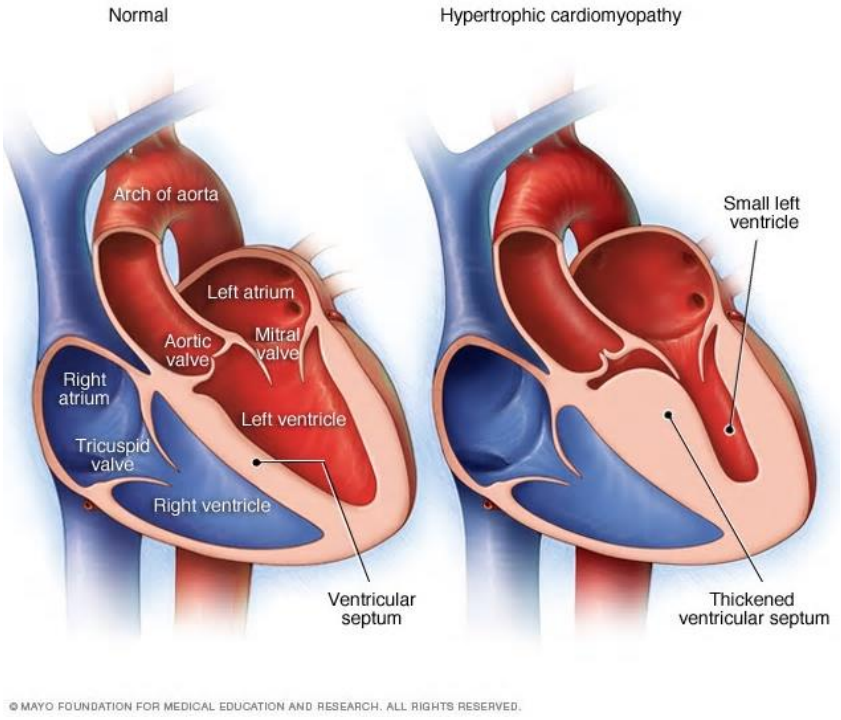
* Effect of Ca channel blockers in angina (verapamil & diltiazem):

1) ↓ impulse generation in the SA node & ↓ conduction in the AV node ➞ ↓ heart rate ⇨ ↓ heart O2 requirements.

2) ↓ contractility ⇨ ↓ heart O2 requirements.

3) Mild coronary vasodilatation (esp in vasospastic angina)

4) Mild inhibition of necrosis & platelet aggregation



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Side effects of CCBs:

1) Hypotension

2) Cardio-depression (bradycardia, heart block, cardiac arrest)

3) Reflex tachycardia (with dihydropyridines)

4) Gingival hyperplasia (esp nifedipine)

5) Ankle edema (vasodilatation)

6) Constipation

- Normal cardiac output = 4-8 L/min.
- Normal stroke volume = 70 ml (End diastolic volume =120 ml)

Contraindications of verapamil & diltiazem:

1) Wolff-Parkinson-White SPW syndrome (atrial re-entry).

In WPW, there is a congenital accessory conducting pathway (bundle of Kent) that re-enters the signal back from the ventricles to the SA node and atrium.

Verapamil & β blockers & adenosine & digoxin cannot be used here because they block the normal conduction pathway and thus stimulate the abnormal re-entry. However, amiodarone or laser ablation of the abnormal fibers are used.

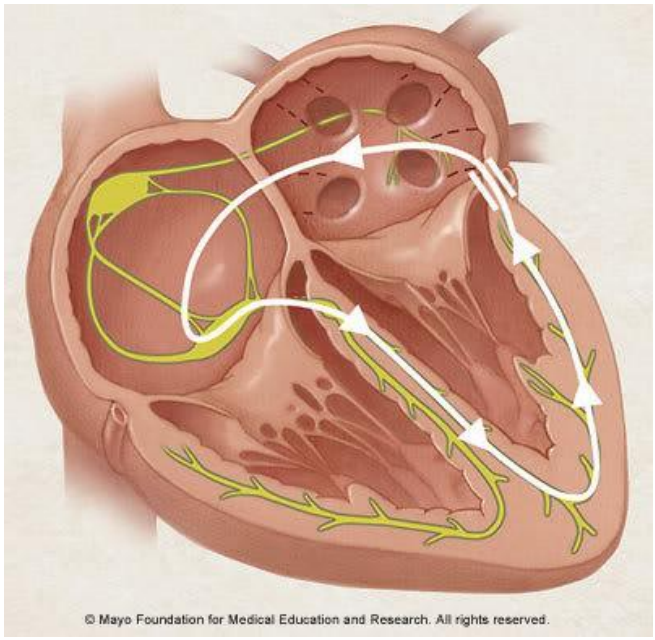
2) CHF or bradycardia

3) With β blockers or digoxin (may cause severe bradycardia)

Contraindications of vasculo-selective CCBs (nifedipine):

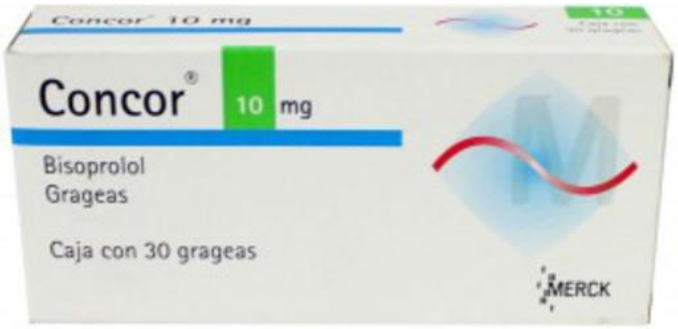
(Due to the reflex tachycardia)

1) Supra-ventricular tachycardia (arrhythmia)
2) HOCM
3) Unstable angina



Wolff-Parkinson-White syndrome

SQUIBB
List 45260
CAPOTEN™ TABLETS
25 mg
20 Tablets
Captopril


Concor®
10 mg
Bisoprolol
Grageas
Caja con 30 grageas
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Tabletas
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PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
100 Tablets
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ISOPTIN® 80mg
VERAPAMIL HYDROCHLORIDE
80mg

* Angiotensin Antagonists

1) Angiotensin Converting Enzyme Inhibitors (ACEIs):

Short → Captopril.(short, 1×3)

Long → Lisinopril, enalapril, ramipril, quinapril, fosinopril. (1×1)

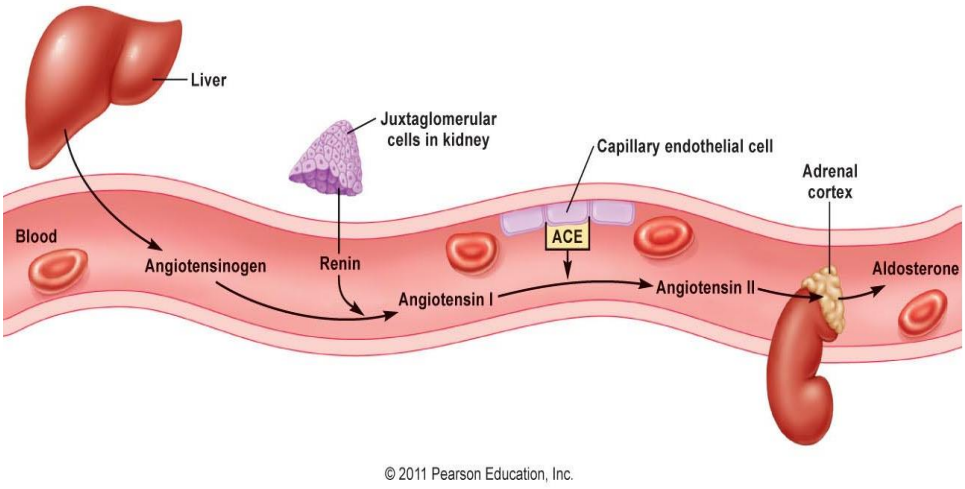
2) Angiotensin receptor blockers (ARBs; block AT1):

Losartan, valsartan, telmesartan, candesartan

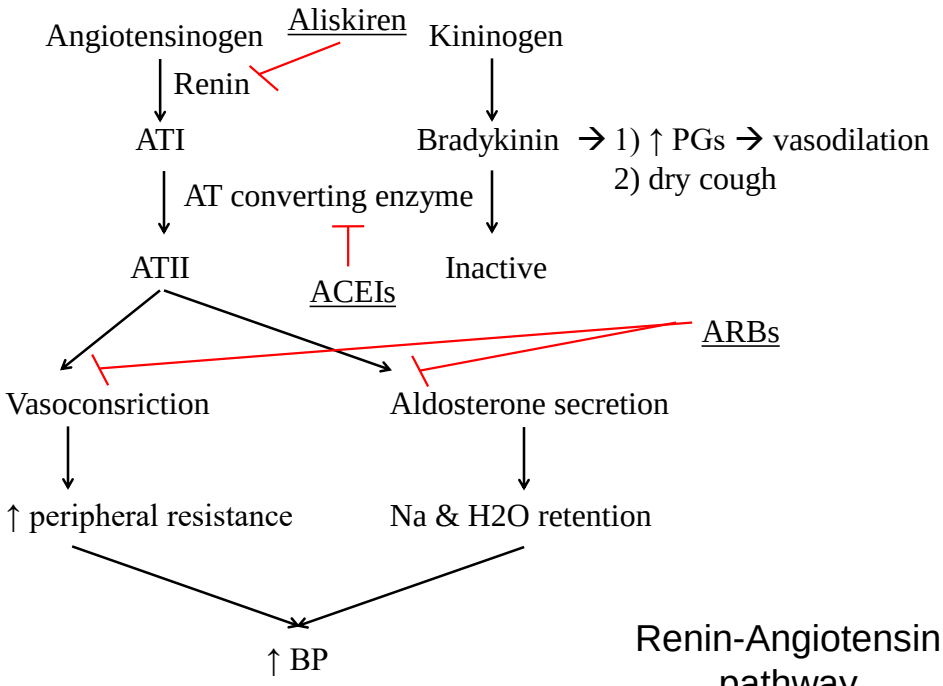
(also irbesartan, olmesartan, eprosartan)

Notes:

* ACE is a dipeptidyl peptidase because it cuts off a dipeptide containing 2 amino acids from AT I which contains 10 amino acids (decapeptide) to form ATII which contains 8 amino acids (octapeptide)
* ATR1 is found in blood vessels and in the adrenal cortex (linked to Gq)
* ATR2 function is unknown (may cause vasodilatation)
* Lisinopril has an additional cardiac depressant effect.



Renin-angiotensin pathway



Renin-Angiotensin pathway

3) β blockers

☺ Role in treating CHF:

1) ↓ β1 in the heart → ↓ cardiac work (esp in CHF caused by overload)
   - ➡ 👍 ↓ activation of lysosomal enzymes.
   - ➡ ✌ ↓ fibrosis.
   - ➡ 👌↓ cardiomegaly → ↓ heart need for O2.

2) ↓ β1 in the kidney → ↓ renin → ↓ AT II:
   - ➡ 👍 vasodilation.
   - ➡ ✌ ↓ aldosterone → ↓ H2O/Na retention.

3) Allows more time for heart filling in diastolic heart failure.

4) ↓ anxiety.

☹ Disadvantage:
Contraindicated in severe cases of CHF because they:

1) ↑ congestive symptoms.

2) ↑ Ischemic symptoms.

3) May cause bradycardia, heart block or cardiac arrest.

Q) Which β blockers are preferred in CHF?
Studies have shown that:
bisoprolol, carvedilol, metoprolol & nebivolol → ↓ mortality

4) Positive Inotropic Agents

☺ Role in treating CHF:
They ↑ heart contractility ➡ ↑ cardiac output which leads to:

1) ↑ rapid improvement in congestive symptoms

2) ↑ rapid improvement in ischemic symptoms.

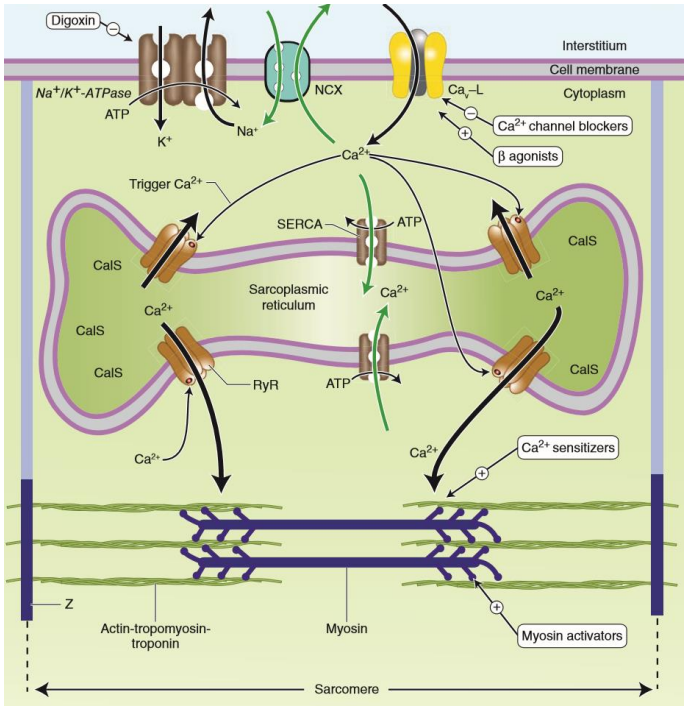
3) ↑ renal perfusion → ↑ diuresis → ↓ blood volume → ↓ preload.

4) ↑ blood flow to the brain → ↓ symp. stimulation (↓ RAAS)

☹ Disadvantages:

1) May cause arrhythmias.

2) ↑ heart work → ↑ lysosomal enzymes, fibrosis, cardiomegaly



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A) β1 agonists

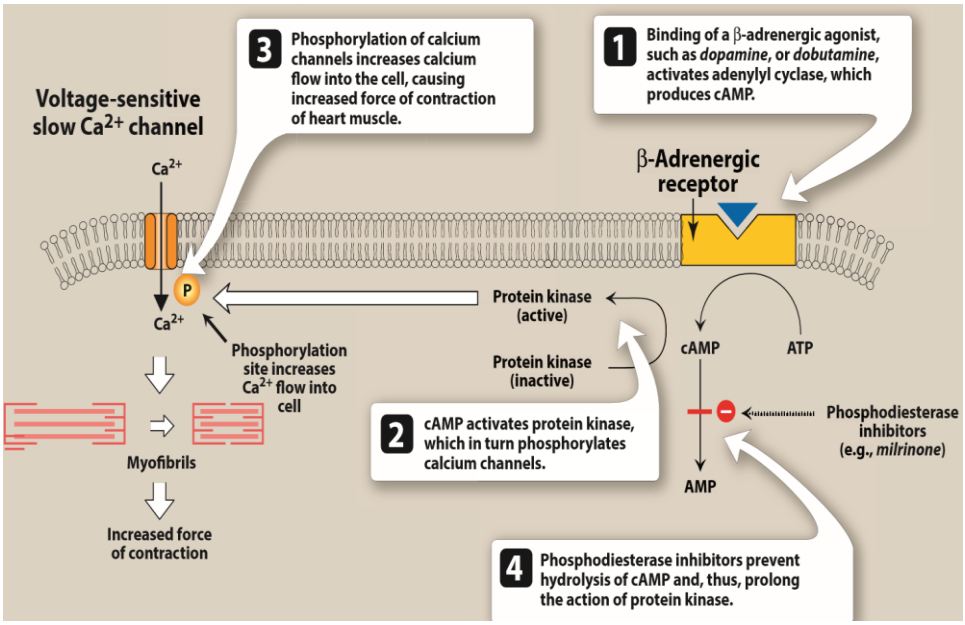
M.O.A:

↑ β1 receptors ⇨ ↑ cAMP in cardiomyocytes ⇨ ↑ opening of Ca channels in cardiomyocytes ⇨ ↑ Ca entry ⇨ ↑ contractility.

Classification:

1) Selective β1 agonists
   * short acting → dobutamine (i.v.)
   * long acting → doxaminol, prenalterol, xamoterol (oral)

2) Non-selective β1 agonists
   (stimulate α1 at high dose ⇨ ↑ preload & afterload ☹).
   * short acting → dopamine (i.v.)
   * long acting → ibopamine (oral)


3 Phosphorylation of calcium channels increases calcium flow into the cell, causing increased force of contraction of heart muscle.
1 Binding of a β-adrenergic agonist, such as dopamine, or dobutamine, activates adenylyl cyclase, which produces cAMP.
Voltage-sensitive slow Ca2+ channel
β-Adrenergic receptor
Ca2+
P
Ca2+
Protein kinase (active)
Protein kinase (inactive)
cAMP
ATP
Phosphorylation site increases Ca2+ flow into cell
2 cAMP activates protein kinase, which in turn phosphorylates calcium channels.
Phosphodiesterase inhibitors (e.g., milrinone)
Myofibrils
AMP
Increased force of contraction
4 Phosphodiesterase inhibitors prevent hydrolysis of cAMP and, thus, prolong the action of protein kinase.

Lippincott 2015

Advantages of Dopamine & Dobutamine:

If given in the right dose, they can be selective (can ↑ contractility without ↑ heart rate).

Disadvantages of Dopamine & Dobutamine:

1) Short acting.

Rapidly metabolized by MAO & COMT → only i.v.

2) Dopamine needs fine dose adjustment.

- In small dose → ineffective
- In large dose → tachycardia & vaso-constriction

3) Rapid tolerance.

Due to down-regulation of β1 receptors → not used long-term.

B) Ca sensitizors

M.O.A:

↑ sensitization of (actine & myosine) to Ca → ↑ contractility.

Agent:

Levosimendan (i.v. infusion diluted with 5% glucose)

Use:

Acute decompensated CHF.

(Not approved yet in the USA but used in 60 other countries)

C) Phosphodiesterase (PDE) inhibitors

What is Phosphodiesterase?

- ATP is converted into active cAMP by adenyl cyclase.
- "cAMP" is active. It stimulates the heart by opening Ca channels in the cell membranes of cardiomyocytes.
- cAMP is degraded by "phosphodiesterase" into inactive AMP.

M.O.A of Phosphodiesterase (PDE) inhibitors:

↓ "phosphodiesterase III" in the heart ⇨ ↑ cAMP:

→ ↑ opening of Ca channels in cardiomyocytes.

→ ↑ Ca entry ⇨ ↑ myocardial contractility.

a) Non-specific → e.g. Aminophyllin (i.v.).

b) Specific PDE III inhibitors → e.g. Amrinone (i.v.; short) & Milrinone (i.v.; longer)

(Melrinone is added to standard therapy in refractory CHF).

D) Cardiac Glycosides (e.g. digoxin)

Old toxic drugs but still used because they are effective and there is no better alternatives.

Source:

Derived from plants like digitalis, strophanthus, squill, oleander.

The most widely used is digoxin which is isolated from the leaves of "Foxglove" (digitalis).

M.O.A:

1) ↓ Na/K pump.

Compete with K^+ on its binding site on the Na/K pump:

→ ↓ neighboring Na/Ca pump.

→ ↑ Ca concentration inside cardiomyocytes ⇨ ↑ contractility.

(* so cardiac glycosides → ↑ intracellular Na, Ca & ↑ extracellular k)

2) ↑ vagal center (in CNS) → ↓ heart rate & conduction

More about Digoxin (Lanoxin®)

Advantageous effects on the heart:

☺ Increase heart contractility → ↓ ischemic symptoms

☺ Increase heart contractility → ↓ congestive symptoms

☺ Increase blood flow to the brain → ↓ symp stimulation

☺ Increase blood flow to kidney → diuresis → ↓ RAAS system

☺ Vagal stimulation in the medulla oblongata → ↓ heart rate

But disadvantages my occur:

☹ Arrhythmia

(formation of ectopic foci due to increased intracellular Na+ → any type of arrhythmia)

☹ Bradycardia (prolongation of PR wave)

☹ More heart work → ↑ O2 consumption

→ ↑ fibrosis, hypertrophy, cardiomegaly.

Main uses of digoxin (oral or rarely slow i.v.):

1) Added in CHF if diuretics & ACEIs (vasodilators) are not sufficient (3rd line drug in heart failure)

2) Atrial fibrillation & atrial flutter
(the most common indication for digoxin; but β blockers & CCBs are preferred)

3) Heart failure with AF (atrial flutter or fibrillation)
Digoxin is the 1st choice because it inhibits the conduction of abnormal supraventricular beats to the ventricles. It also causes bradycardia.

Side effects of digoxin:

1) ↑ heart → arrhythmias (e.g. bigeminy).

2) ↑ brain at the vagus nucleus → heart block

3) ↑ brain at other centers → confusion, yellow vision, vomiting.

4) ↑ GIT smooth muscles → diarrhea/colic

5) Gynecomastia (has a steroid structure similar to estrogen))

Absolute Contraindications:

- Some arrhythmias (e.g. heart block)

Notes:

* In the past, digoxin used to be given 5-6 days a week with 1-2 days with no dosing (to allow the body to excrete the drug and avoid toxicity). That's rarely done nowadays.

* Digoxin is not injected i.m. due to severe pain & necrosis.

* How to administer digoxin:

Loading dose (rapid digitalization) followed by maintenance doses in atrial fibrillation (rapid digitalization is not necessary in CHF). We use loading doses because digoxin accumulates in all muscles before acting on the heart muscle , so we need to saturate other muscles first.

Digoxin interactions:

1) Digoxin is excreted by tubular secretion by P-glycoproteins.
So P-glycoprotein inhibitors + digoxin → ↑ digoxin toxicity.
(e.g. quinidine, spironolactone, verapamil, amiodarone)

2) Thiazides/ Loop diuretics → hypokalemia → ↑ digoxin toxicity

3) Digoxin + erythromycin or tetracycline → ↑ digoxin toxicity!
(some digoxin is normally reduced by some intestinal flora into an inactive metabolite).

Notes:

- K levels need to be monitored during digoxin therapy
- Hypertrophy vs hyperplasia:
  - Hypertrophy = increased size of tissue due to enlargement of cells.
  - Hyperplasia = increased size of tissue due to increased number of cells.

Notes on digoxin poisoning & treatment:

Symptoms:

Confusion, diarrhea, abdominal pain, vomiting, lethargy, yellow vision, fatal arrhythmia (almost any type of arrhythmia may occur)

Signs:

Hyperkalemia, ECG changes (skipped ST waves)

Risk factors:

Hypokalemia, hypercalcemia

Treatment:

1- Activated charcoal (within hours of ingestion)

2- Atropine for bradycardia; phenytoin, lidocaine or MgSo4 for premature ventricular arrhythmias

3- “Digoxin-specific antibody fragment” (digoxin immune Fab; Digibind®) only for severe toxicity. (until Fab is acquired, phenytoin, lidocaine or magnesium can be used to treat the arrhythmias)

- Digoxin use declined since the 1990s.
- Chronic toxicity is far more common than acute toxicity.

The powder is reconstituted in 4 ml water then diluted further in normal saline and infused over 30 min.
(FAB = fragment antigen binding)

5) New Drugs

(natriuretic peptides modulators)

a) Nesiritide (i.v.):

- A recombinant B-type natriuretic peptide approved for:
  → acute heart failure in hospitalized patients
- Carperitide is a recombinant ANP (used only in Japan)

☹ Both nesiritide & carperitide are not very promising.

b) Neprilysin inhibitors (sacubitril):

- Neprilysin is a membrane-bound endopeptidase (in some tissues esp. in the kidney) that degrades natriuretic peptides
  [also degrades ATII so Neprilysin inhibitors must be given in combination with ARBs; called "angiotensin receptor neprilysin inhibitor" (ARNI)]
- Usually given in combination with valsartan (in the same tablet)

* Nerpilysin inhibitors are not combined with ACEIs because neprilysin also degrades bradykinin. This will increase bradykinin levels by both drugs and may increase incidence of angioedemas and dry cough.

What are natriuretic peptides? (cardio-neuro-hormones)

3 hormones that ↑ Na/H2O diuresis → ↓ BP

(they also ↓ sympathetic system & renin-AT system & ↓ salt appetite centrally)

- Net effect is ↓ preload & afterload → good for hypertension & heart failure.

1) A-type: Secreted by the atria (in response to stretch or ↑ BP)
   - Previously called atrial natriuretic peptide (ANP)

2) B-type: Secreted by the ventricles (in response to stretch or ↑ BP)
   - previously called "brain natriuretic peptide" (BNP)

3) C-type: Secreted by the lung & kidney (in response to stretch or ↑ BP)

- The natriuretic peptides oppose the detrimental effects of RAAS.

- Neprilysin degrades: natri-uretic peptides, AT II & bradykinin

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Chapter 2

Anti-hypertensive Drugs

Blood pressure (BP)

The tension exerted by the blood on the vessel wall.

- There are 2 blood pressures to measure:
  - Systolic BP ⇨ 120 mmHg normally.
  - Diastolic BP ⇨ 80 mmHg normally.

What is systolic blood pressure?

During systole: The heart ejects blood through arteries leading to relatively high BP (this BP is called systolic blood pressure)

What is diastolic blood pressure?

During diastole: No blood is ejected by the heart. The arteries recoil to prevent BP fall (this BP is called diastolic blood pressure)

Factors increasing BP

1) ↑ Cardiac Output.

2) ↑ Peripheral resistance.

3) ↑ Blood volume.

Cardiac output:

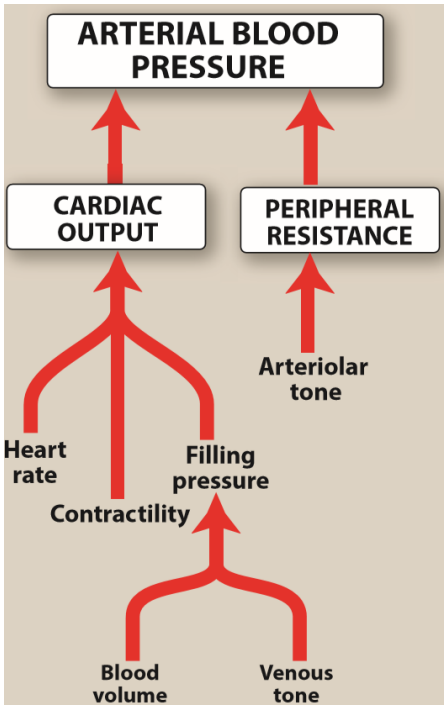
The volume of blood pumped by the heart in 1 minute.

(stroke volume is the volume of blood pumped by the heart in 1 heart beat)

Peripheral resistance:

The resistance of walls of peripheral arteries to blood flow.

Factors affecting blood pressure



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Control of BP

A) Rapid control (Neurological):

1) Stretch of vessel wall:

Stretch → ↑ baroreceptors which sends a message to the CNS.

→ ↑ the hypothalamus to send neuronal messages to cause:

- reflex vasodilatation & bradycardia.

2) Brain or muscle ischemia (due to excessive vaso-constriction)

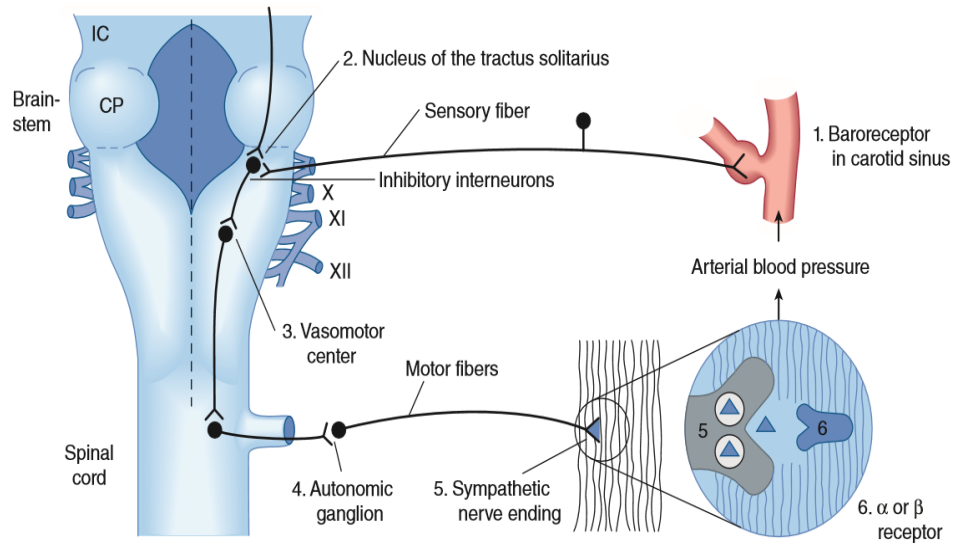
Ischemia → ↑ hypothalamus to send messages to cause:

- reflex vasodilatation & bradycardia.

3) Emotions:

Cause variable response:

- Some people may have ↑ BP.
- Some people may have ↓ BP (may lead to neurological shock)



11–2 Baroreceptor reflex arc. IC, inferior colliculus; CP, cerebellar peduncle.

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B) Intermediate control (Kidney control)

Renin secretion:

↓ BP (e.g. due to ↓ sympathetic activity or ↑ Na+ in urine)

→ ↑ renin secretion from kidneys:

Renin-angiotensin-aldosterone system (RAAS):

1) Renin coverts “angiotensinogen” into “angiotensin I”

2) Then ACE converts “angiotensin I” into “angiotensin II”

3) Then angiotensin II binds its receptors (ART1) to cause :

a - vasoconstriction.

b - ↑ aldosterone from the adrenal cortex

⇨ stimulates Na+/k+ pump in distal tubule

→ H2O & salt retention

C) Slow control (hormonal; e.g. ADH):

To clarify it, let’s compare increased salt intake vs H2O intake:

1) ↑ salt intake:

⇨ ↑ osmotic pressure ⇨ ↑ Osmoreceptors in hypothalamus

⇨ ↑ neuronal firing to ↑ ADH secretion (from the pituitary)

⇨ ↑ H2O reabsorption from the collecting duct

⇨ ↑ Blood volume → ↑ BP.

2) ↑ water intake:

↑ blood volume (↑ BP)

⇨ ↑ renal blood flow

⇨ ↑ GFR

⇨ ↑ urine

⇨ ↓ Blood volume → ↓ BP.

Notes:

* Isolated systolic hypertension in the elderly:

= systolic blood pressure is elevated (> 140) with a normal (< 90) diastolic blood pressure (DBP).

Cause:

↓ compliance of the aorta with increasing age.

(leading to ↓ coronary blood flow, left ventricular hypertrophy, heart failure)

Goal of treatment:

To reduce systolic BP to 140 as long as diastolic BP is > 68.

Drugs of choice:

- Thiazides
- CCBs (dihydropyridines)
- ACEIs or ARBs

Types (causes) of Hypertension:

1) Primary Hypertension: (essential hypertension)

- 85-90% of cases.
- Not a complication of another condition or disease.
- Result from multiple factors like:
    - ↑ blood volume
    - abnormal hormonal activity
    - ↑ stress
    - lack of exercise

A. high-renin hypertension.

Due to ↑ renin activity.

B. low-renin hypertension.

Due to ↑ H2O & salt retention.

2) Secondary Hypertension:

10-15% of cases. Occurs as a result of some diseases or drugs:

➡ Renal hypertension:

Usually due to chronic renal failure.

➡ Renovascular hypertension:

Due to a stenosis in the renal artery

⇨ ↓ urine formation

⇨ ↑ blood volume.

➡ Endocrine hypertension:

Tumors secreting adrenalin (Pheochromocytoma) or cortisol (Cushing disease) or growth hormone (Acromegaly)

➡ Drug-induced hypertension:

NSAIDs, corticosteroids, contraceptives, sympathomimetics, sex hormones….etc.

Diagnosis:

By measuring BP. (not by symptoms)

Symptoms:

No symptoms. (silent till complications occur!)

So the hypertensive patient has to make a choice between:

1) Taking medicines and enduring cost & side effects of drugs to prevent consequent complications.

2) Not taking medicines since there are no symptoms.

* Best drugs for emergency hypertension:

1. Na nitroprusside (i.v. infusion, drug of choice)
2. Labetalol i.v. (good alternative)
3. Others: diazoxide, hydralazine, phentolamine, nitroglycerin

Complications:

- Rapid increase in BP:
  - ⇨ Hemorrhage (cerebral, retinal, epistaxis…)

- Slow increase in BP:
  - ⇨ ↑ afterload → Heart failure.
  - ⇨ Arterioles' resistance to blood flow to organs
    - → tissue ischemia:
      - ☒ brain → confusion.
      - ☒ kidney → renal failure.
      - ☒ limbs → peripheral vascular diseases.

Degrees of Hypertension:

	Systolic BP (mmHg)		**Diastolic BP** (mmHg)
Normal	**< 120**	**and**	**< 80**
Elevated	**120 - 129**	**and**	**< 80**
Stage I hypertension	**130 - 139**	**or**	**80 - 89**
Stage II hypertension	**> 140**	**or**	**> 90**
Hypertensive crisis (emergency hypertension)	**> 180**	**or**	**> 120**

* Malignant hypertension:
Is a sudden & severe increase in BP → possible hemorrhages

Therapy:

1) Non-drug therapy:
- ↓ weight
- ↓ Na+ intake
- ↓ fat intake
- Exercise
- Smoking cessation

2) Drug therapy:

Using drugs to achieve the following:
- ↓ Blood volume.
- ↓ Cardiac output.
- Vasodilatation (→ to ↓ arterioles resistance & ↑ veins capacity)

Anti-hypertensive Drugs

- A) Diuretics
- B) Sympatho-lytics
- C) Vasodilators

For hypertension in pregnancy:
1) The preferred drug is α-methyl dopa.
2) Labetalol & nifidepine are also used in maintenance therapy
3) Hydralazine is another choice in emergency hypertension.

A) Diuretics

Role in BP:

1) ↓ blood volume (rapid)
2) ↑ release of vasodilator PGs (PGE2 & PGI2) ⇨ VD (slow)
   (→ ↑ GFR & urine volume & also ↓ peripheral resistance of b. vessels)

- Loop diuretics:

- Best for emergency cases! but can also be used long-term

- Thiazides

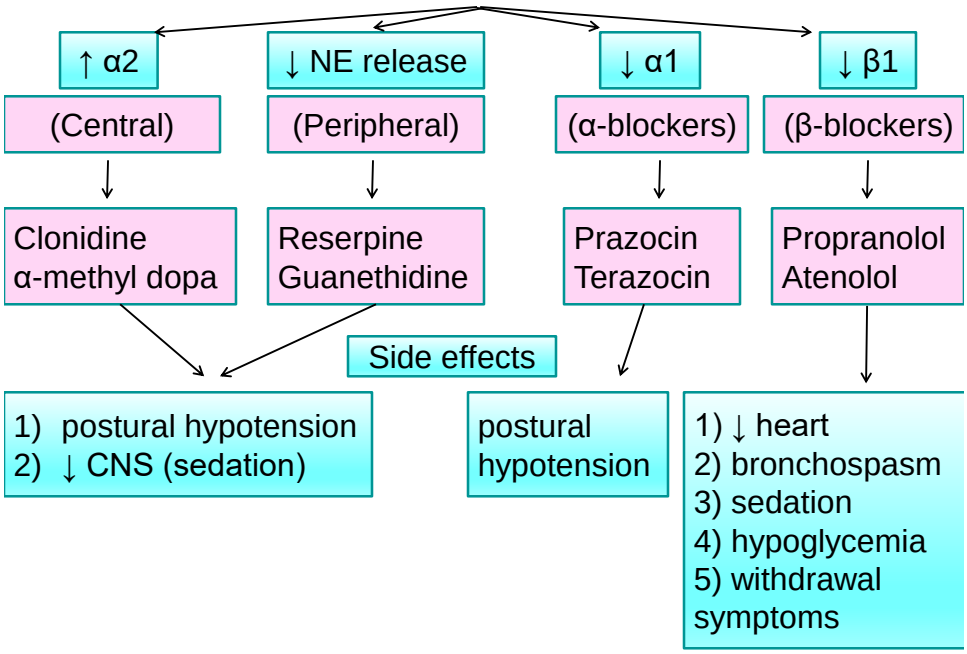
- Used for long-term therapy

(Hydrochlorothiazide is one of the most commonly drugs for hypertension)

- Potassium-sparing diuretics:

- With strong diuretics (loop or thiazides) to preserve K+.

B) Sympatholytics



a- Centrally-acting α2 stimulants

- Clonidine: (oral & TDS patch)

MOA:

1. ↑ α2 in brain stem → ↓ symp. outflow from CNS → vasodilation.

2. ↑ α2 presynaptically → ↓ NE release from nerve terminals.

☹ Side effects:

1) CNS: sedation, depression

2) Orthostatic hypotension

3) Sudden stoppage → may cause rebound hypertensive crisis.

* It initially ↑ BP due to ↑ α2 in b. vessels (esp if given i.v.)

- α-methyldopa (oral, i.v.)

A prodrug [α-methyldopa (prodrug) → α-methyl-NE (active)]

MOA:

Like clonidine.

Use:

Hypertension (esp in pregnancy)

Side effects:

1) CNS → sedation, ↓ concentration, depression

2) Orthostatic hypotension

3) ↓ Dopamine synthesis:

→ parkinsonian symptoms

→ ↑ prolactin release → ↓ FSH & LH

b) ↓ NE release from nerve ending

Reserpine & Guanethidine

MOA:

↓ NE release from nerve ending

Reserpine can also ↓ NE centrally → CNS side effects like depression
Guanethidine cannot pass BBB → no CNS side effects

Side effects:
The 2 drugs are rarely used due to side effects:
- reserpine → severe depression!
- guanethidine → severe orthostatic hypotension!

(Their side effects may be blocked by tricyclic antidepressants!)

Drug	MOA
Reserpine	↓ the vesicle NE uptake pump in the symp nerve terminal → NE depletion
Guanethidine	Accumulates inside nerve NE terminal vesicles → ↓ NE release
Bretylium & Guanadrel	↓ NE release

Detailed Drug mechanisms

c) α1 blockers

Prazocin, terazocin, doxazocin (oral).

MOA:

↓ α1 → vasodilation → ↓ BP

Side effects:

1) 1st-dose phenomenon (severe hypotension with 1st dose)
2) Orthostatic hypotension (so start with a low dose & at bedtime)

d) β-blockers:

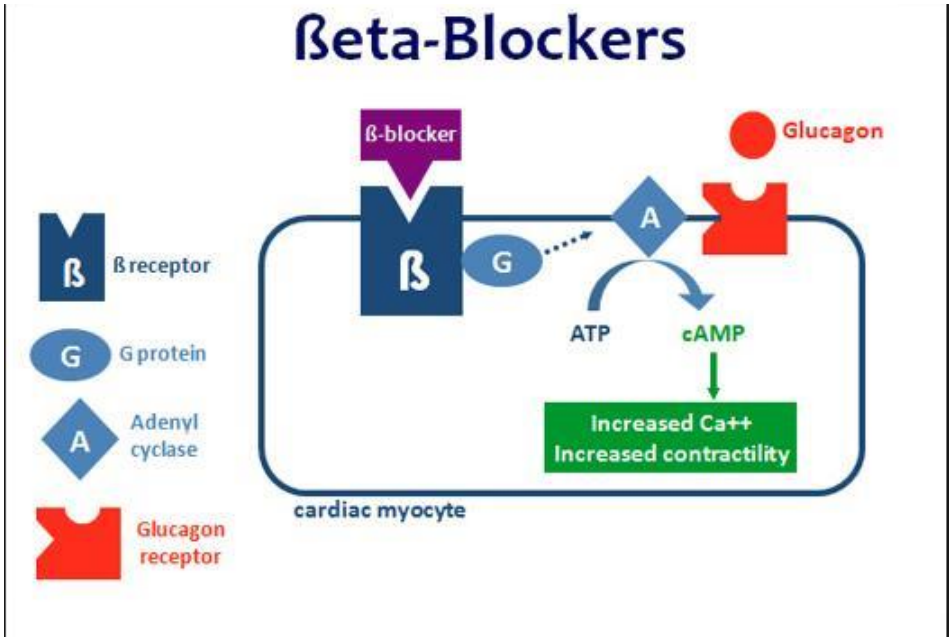
MOA:

↓ β1:

→ ↓ heart rate & contractility → ↓ cardiac output

→ ↓ renin release → vasodilation & ↓ H2O/Na+ retention

(see next figure)



β-blockers are adrenergic receptor antagonists

Classification of β blockers

1st gen. (non-selective) (non-selective β1 & β2)	2nd gen. (cardio-selective) (selective β1 blockers)
Propranolol	Atenolol
Timolol	Acebutolol
Pindolol	Bisoprolol
Nadolol	Betaxolol
Sotalol	Metoprolol
	Esmolol

3rd generation (vasodilator β-blockers)

Non-Selective (↓β1 & β2 & α1)	Selective (↓β1 & ↑ NO)
Carvedilol	Nebivolol
Labetalol	
Bucindolol	

Side effects:

1) Block β1:
   → ↓ heart contractility → may worsen heart failure at times
   → bradycardia

2) Block β2:
   → bronchospasm

3) ↓ CNS → sedation

4) Hypoglycemia or hyperglycemia

5) Withdrawal → ↑↑↑ BP, angina, MI!
   (so gradual tapering is recommended)

Notes:

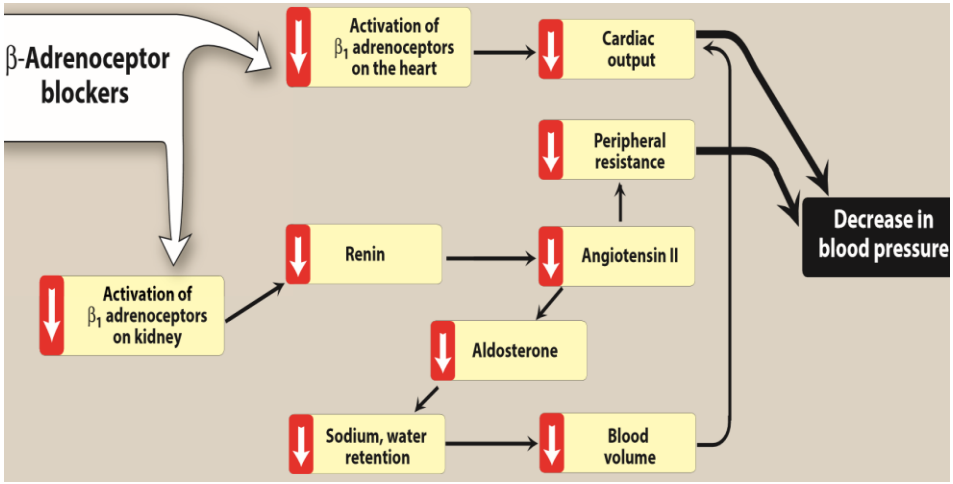
* There are β blockers that are actually partial agonists on β1 "have intrinsic sympathomimetic activity" → less cardio-depressant effect:
   1) Acebutolol
   2) Labetalol
   3) Pindolol

Advantage:
Preferred in patients with pre-existing bradycardia or heart block.

* African Americans are more prone to hypertension and combination therapy is thus preferred. But if monotherapy is needed, remember that ACEIs & ARBs & beta blockers are weak in African Americans (work in some but weak in others). However, a thiazide or a CCB is effective as a monotherapy. (Importance of RAAS and renin level is lower in African Americans).

* Although African Americans do not respond well to ACEI monotherapy, they do respond to therapy with ACEIs combined with diuretics.

* Best drugs for hypertension in diabetics → ACEIs.



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How β blockers decrease blood pressure

C) Vasodilators

a) Arteriolar Dilators:

- Hydralazine: (Apresoline®; oral or parenteral)

MOA: (not 1st choice due to reflex tachycardia; ☺ Good in pregnancy)

↑ NO release → Arteriolar dilator

→ ↓ peripheral resistance → ↓ BP

* In slow-acetylaters → drug-induced lupus-like syndrome may occur (the drug is partly metabolized by acetylation)

- Minoxidil [oral; minoxidil → minoxidil sulfate (active)]

↑ opening of K+ channel → hyperpolarization of smooth muscle cells (in blood vessels) → vasodilation

Specific SEs:

1) ↑ hypertrichosis (↑ hair growth!; used commonly for that purpose!)

2) Pericardial effusion (rare but serious!)

- Fenoldopam (i.v. infusion for hypertensive emergency)

MOA:

↑ D1 → vasodilation

(↑ D1 → ↑ Gs → ↑ Adenyl cyclase → ↑ cAMP → ↓ myosin light chain kinase → vasodilation)

Route: continuous i.v. infusion (due to rapid metabolism)

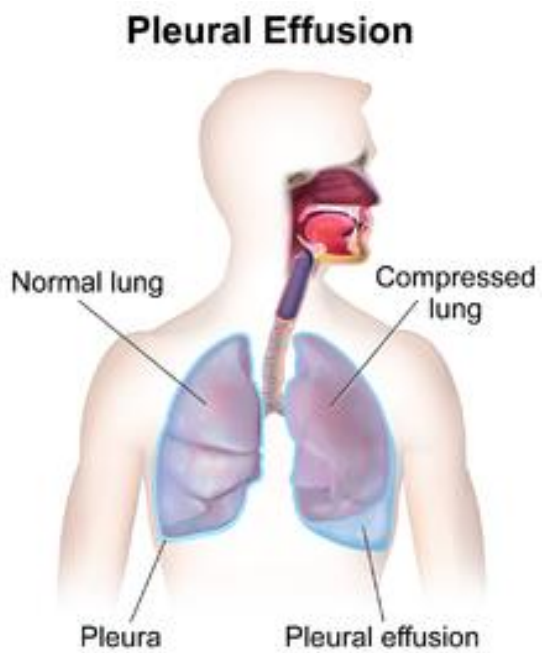
- Diazoxide (oral or i.v. inj for hypertensive emergency):

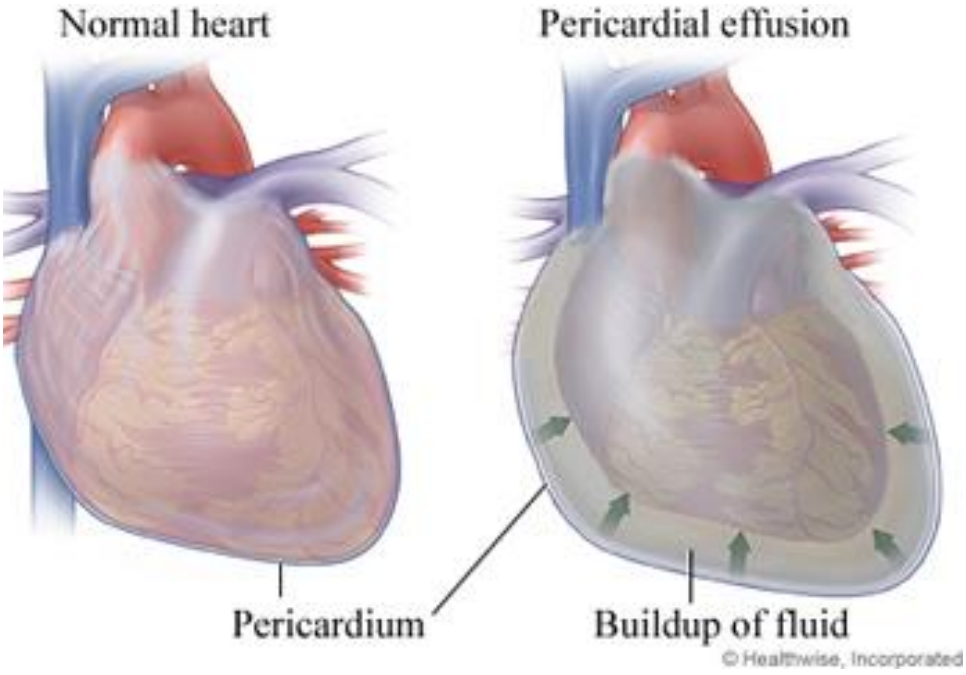
MOA: Like Minoxidil

SE: ↓ insulin release → not used long term.

(opens K channels in β cells)

* Pleural effusion = a lot of fluid in the pleural cavity → ↓ lung expansion
(Pneumothorax = too much air in the pleural cavity → ↓ lung expansion. It results either from internal rupture of alveoli or from an external stab or injury)





Adverse Effects of Vasodilators:

1) Vasodilation:

→ ↓ BP

→ in brain: headache

→ In eye: ↑ IOP, eye redness

→ In nose: stuffy nose

→ In skin: flushing

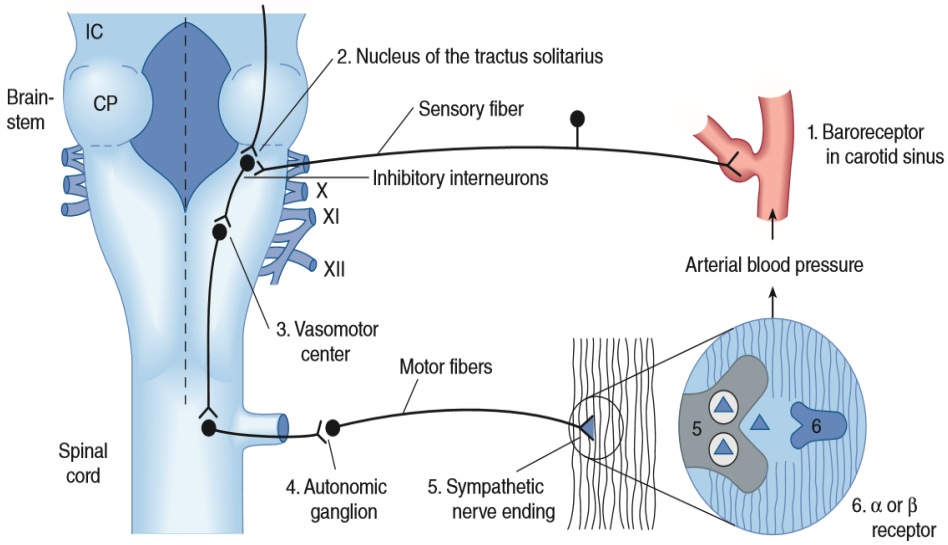
→ In heart: pericardial effusion (rare but serious!)

2) Compensatory sympathetic stimulation (↑β1):

* ↑ heart (compensatory) → palpitation, angina, ECG changes
* ↑ RAAS → Na+/H2O retention (edema)

(so with vasodilators, add diuretics & β-blockers)

- *Fenoldopam, Na nitroprusside & esmolol → short t1/2 → given i.v. infusion*
- *Diazoxide → oral or i.v. for emergencies.*



11–2 Baroreceptor reflex arc. IC, inferior colliculus; CP, cerebellar peduncle.

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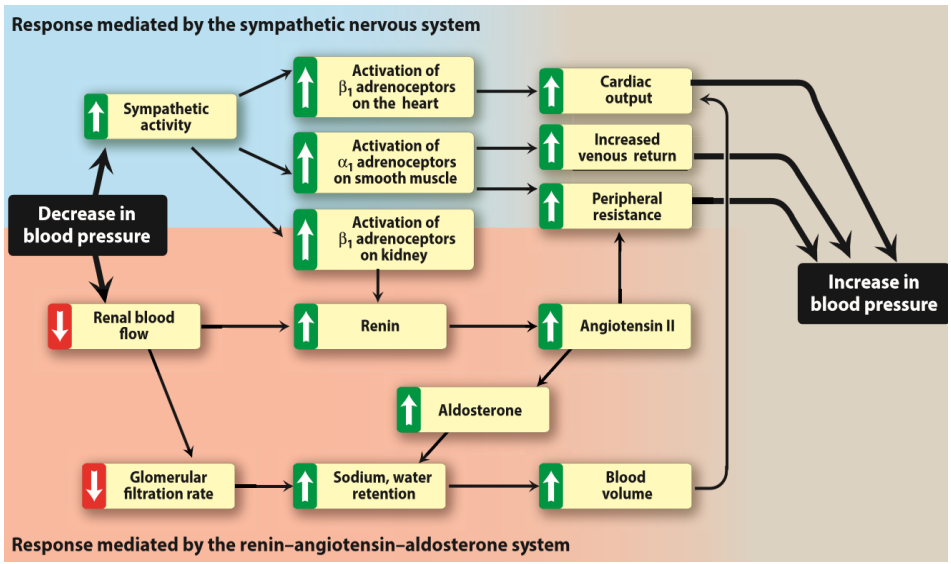

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b) Mixed Arteriolar & Venous Dilators

- Sodium nitroprusside:

Powerful → best for hypertensive emergency (slow i.v. infusion)

MOA:

↑ NO → ↑ guanyl cyclase → ↑ cGMP → vasodilation

Side effect:

Cyanide toxicity (close monitoring is needed)

Notes:

- Drug solution is light sensitive → so protect from light
- Rapid onset & offset → so given continuous i.v. infusion

- Ca Channel blockers:

Di-hydro-pyridines (e.g. nifedipine) are good for hypertension

- Angiotensin Antagonists

a) Direct renin inhibitors:

Aliskiren

b) Angiotensin Converting Enzyme Inhibitors (ACEIs):

Short → Captopril (1×3)

Long → Lisinopril, enalapril, ramipril, quinapril, fosinopril (1×1)

c) Angiotensin receptor blockers (ARBs):

Losartan, valsartan, telmesartan, candesartan

(also irbesartan, olmesartan, eprosartan)

More about ACEIs:

Agents:

Captopril, Enalapril, Lisinopril /lysinopril/, Ramipril, Quinapril, Fosinopril, Benazepril, Trandolapril, Moexipril, Enaliprilat

- Many are prodrugs (all except captopril & lisinopril)
- Oral except enaliprilat (an active metabolite of enalapril) → i.v.

MOA:

↓ ACE → ↓ conversion of ATI to ATII:
→ vasodilation & less H2O/Na retention

* Plasma renin activity increase with ACEIs!
* How to deal with the dry cough of ACEIs?
Give NSAIDs (Aspirin) with the ACEIs or change to ARBs.

Side effects of ACEIs esp captopril include:

1. Cough (shift to ARBs)
2. Angioedema (Give nasotracheal tube to secure breathing, stop drug, give cortisone, adrenaline and anti-histamine, change to ARBs)
3. Proteinurea
4. Taste changes
5. Orthostatic hypotension (1st dose; start with small dose and at night)
6. Pregnancy (contraindicated due to teratogenicity)
7. Rash
8. Increased K+ in plasma
9. Leucopenia

* Icatibant S.C. is a very expensive drug (blocks bradykinin B2 receptors) used to treat sudden attacks of hereditary angioedema in adults with C1-esterase-inhibitor deficiency (the C1-esterase-inhibitor inhibits kallekrein which promotes bradykinin production). However, It is not effective in ACEI-angioedema.

Source: Usatine RP, Smith MA, Mayeaux EJ, Chumley HS: *The Color Atlas of Family Medicine, Second Edition:* www.accessmedicine.com
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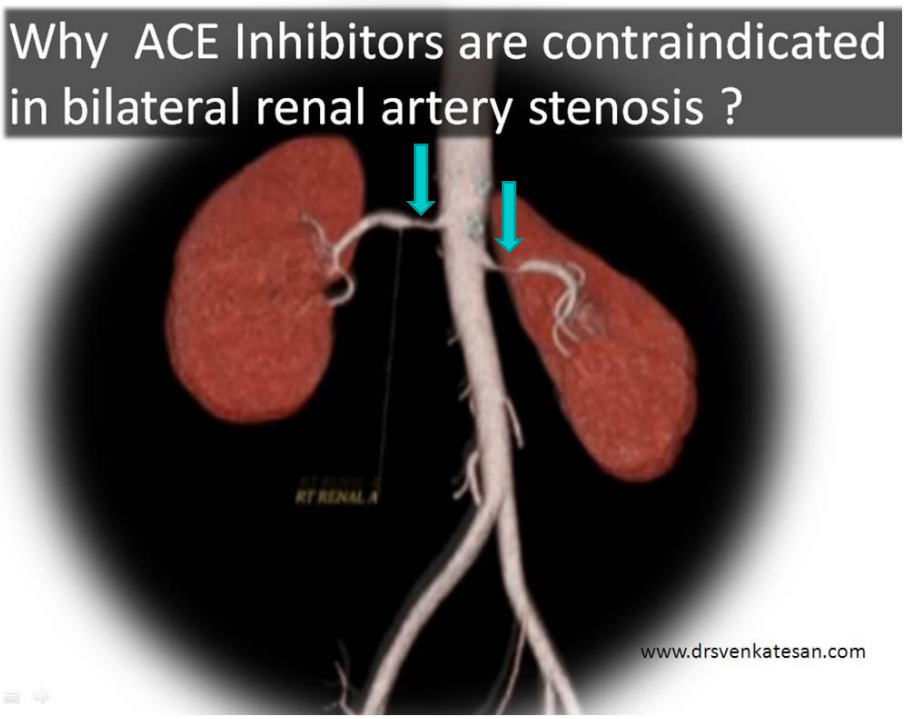
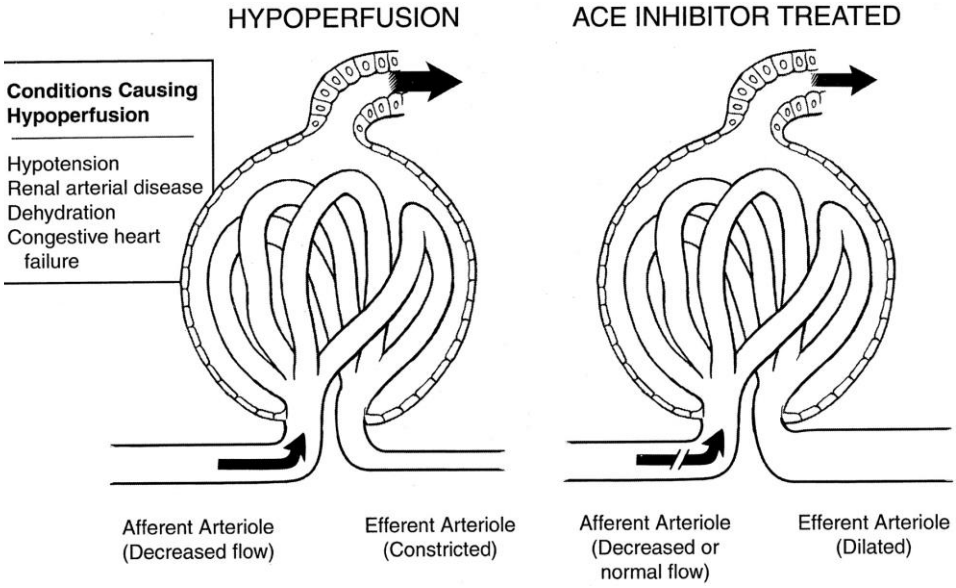
Angioedema





ACEIs may worsen
bilateral renal artery stenosis

- More about ARBs:

Agents (oral)

Losartan, valsartan, telmisartan, candesartan

(also irbesartan, olmesartan, eprosartan)

MOA:

Selectively block ATR1 receptors → vasodilation & ↓ aldosteron

Main Adverse effects of ACEIs & ARBs:

1) Vasodilators → hypotension & angioedema
2) ↓ aldosterone → ↑ K+ in plasma (esp. if with K-sparing diuretics)
3) ↑ bradykinin → dry cough
4) ↓ renal function (esp in patients with bilateral artery stenosis)
5) In pregnancy → teratogenic

On peripheral resistance	On renal function	On CVS structure
→ rapid pressor response	→ slow pressor response	→ hypertrophy & remodeling
MOA:		
1) Direct vasoconstriction	1) ↑ aldosterone → Na & H2O retention	1) ↑ proto-oncogenes 2) ↑ growth factors 3) ↑ ECM proteins
2) ↑ Symp outflow & NE release	2) Renal vasoconstriction	4) ↑ afterload →heart hypertrophy
3) ↑ NE & Epi release from adrenal medulla		5) ↑ wall tension → vascular hypertrophy

Angiotensin II (ATII) Effects

* New drugs for hypertension:
(Endothelin receptor blockers)

New drugs approved for pulmonary hypertension.

They include:

1) Bosentan. (dual: blocks ET-A & ET-B receptors)

2) Ambrisentan. (blocks ET-A receptor selectively)

3) Macitentan. (dual: blocks ET-A > ET-B receptors)

- Endothelin constricts pulmonary blood vessels.
- For idiopathic pulmonary fibrosis, there is no cure. However, 2 drugs are approved to halt the progression of disease (pirfenidone & nintedanib)

Summary of the Main Antihypertensive Drugs

A) Diuretics (Loop diuretics, Thiazides, K-sparing diuretics)

B) Drugs that alter symp. N.S. activity
- central: (clonidine, α-methyl dopa)
- at postganglionic nerve ending: (reserpine, guanethidine)
- receptor blockers:
  - α blockers:
    - non-selective (phenoxybenzamine, phentolamine)
    - α1 selective (prazocin)
  - β-blockers:
    - non-selective (propranolol)
    - β1-selective (metoprolol)
    - α,β blockers (labetalol, carvedilol)

C) Vasodilators:
- Arterial (hydralazine, minoxidil, diazoxide, fenoldopam)
- venous (nitrates: nitroglycerine, isosorbide mononitrate)
- Arterial & venous (Na nitroprusside!)

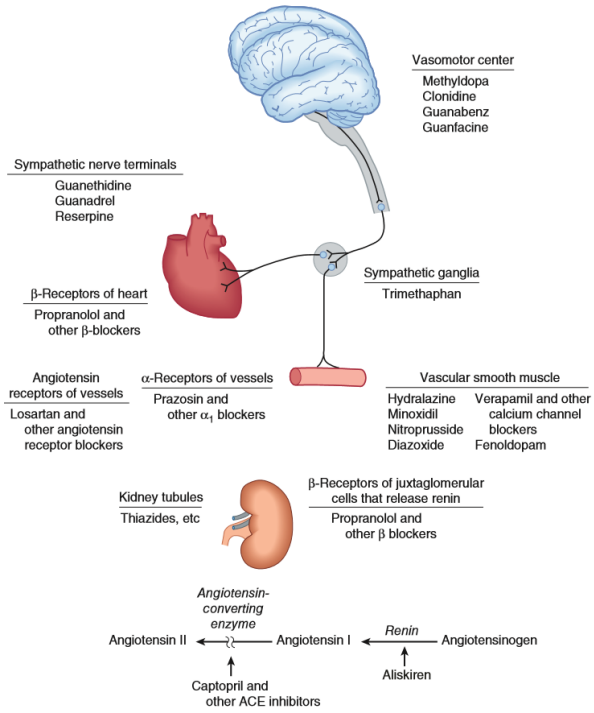
D) Ca channel blockers

E) Renin-angiotensin antagonists:
- Angiotensin converting enzyme inhibitors (captopril)
- Angiotensin receptor blocker (losartan)
- Renin inhibitors (aliskiren)

But remember that the main drugs in hypertension are ABCD:
ACE inhibitors & ARBs, B blockers, CCBs, Diuretics.

* Isolated systolic hypertension (occurs mostly in the elderly)
- Stiffness of the artery walls → ↑ systolic BP (with normal diastolic BP)
- Treated best by: thiazides or ca channel blockers (CCBs)

How all hypotensive drugs work:



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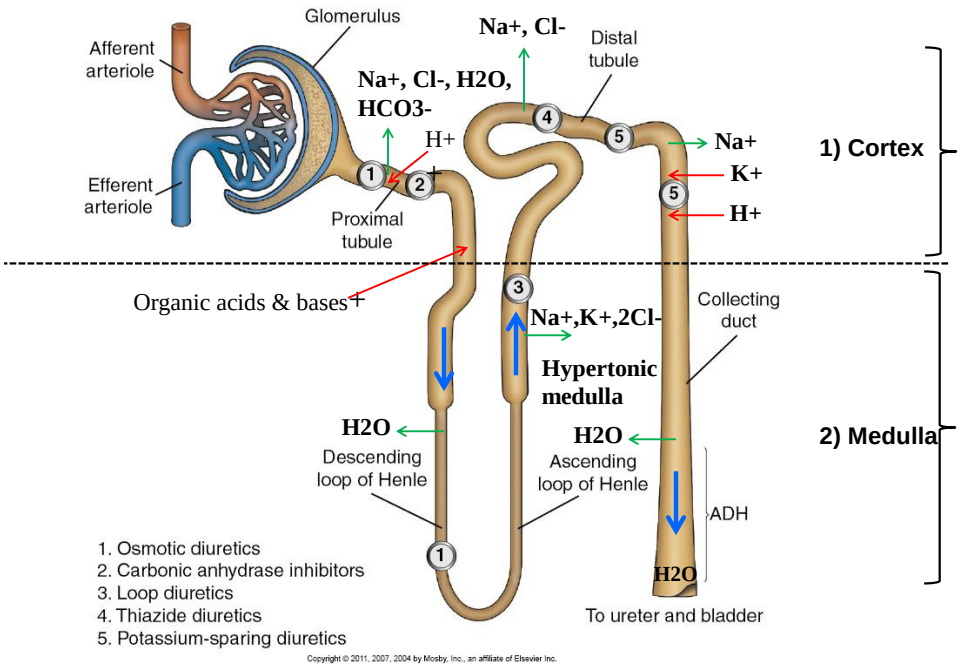
Chapter 3

Diuretics



	1) Proximal tubule	2) Ascending loop of Henle	3) Distal tubule	4) Collecting tubule
Na+ reabsorption	65%	25%	7%	3%
H2O permeability	Permeable	Not	Not	variable
Other notes	1) HCO3 reabsorption 2) Site of secretion for organic acids & bases	1) Medullary fluid becomes hypertonic		1) K+ & H+ secretion occurs 2) Site of action for Aldosterone

Review of Renal Salt and H2O retention

A) Proximal tubule:

1) Principal site of salt & H2O reabsorption.
   - 65% of filtered Na+ reabsorbed
   - HCO3 reabsorption depends on: - carbonic anhydrase &
     - H+ secretion
   - Very high permeability to H2O

2) Site of organic acid & base secretory systems
   (many diuretics are substrates)

Note:
- A diuretic is a drug that increase urine volume
- A natriuretic is a drug that increase Na excretion

B) Thick ascending limb of loop of Henle:

1) 25% of filtered Na+ reabsorbed

2) Very low permeability to H2O which results in:
   → ↑ tonicity of medullary fluid
   → ↓ tonicity of Tubular fluid

C) Distal convulated tubule:

1) 7% of filtered Na+ (& Cl-) reabsorbed
2) Very low permeability to H2O

D) Collecting tubule: (site of action for aldosterone)

1) 3% of Na+ reabsorbed
2) K+ & H+ secretion
3) Variable permeability to H2O (ADH increases this permeability)

Types of Diuretics

1) Osmotic Diuretics: (e.g. mannitol)

MOA:

1) ↑ osmolarity of extracellular fluid & plasma
   → ↑ H2O movement out of cells into plasma
   → ↑ blood volume → ↑ urine

2) ↑ osmolarity of tubular fluid (at the proximal tubule)
   → ↓ osmotic H2O reabsorption

Uses:

1) Diuretic (rarely; e.g. to excrete fluids in acute renal failure)
2) ↓ ICP (intra-cranial pressure) in brain edema.
   (creates a hypertonic plasma to draw water out of the brain)

Side effects

1) Dehydration
2) Dilutional hypernatremia as a result of dehydration.

Notes

* If mannitol crystalizes in low temp → heat it to 60C then cool it.
* Other drugs for brain edema:
  → urea, glycerol & hypertonic saline (2, 3, 5, 7%)

2) Carbonic Anhydrase Inhibitors: (acetazolamide, dorsolamide)

More used in the past but rarely used nowadays.

MOA:

1) Inhibit carbonic anhydrase enzyme in the proximal tubule
   → ↓ $NaHCO_3$ reabsorption

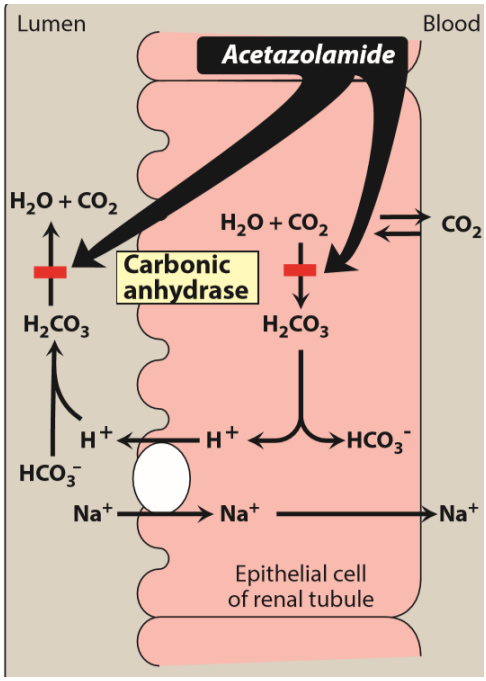
Adverse effect:

- Urine calculi & metabolic acidosis (→ ↓ CNS)

Uses:

1) Diuretic (rare)
2) ↓ IOP (intra-ocular pressure) as eye drops
   (carbonic anhydrase in the ciliary epithelium helps in formation of aqueous humor)
3) Epilepsy (these drugs cause acidosis → depress CNS)
4) For acute mountain sickness before climbing

a- low atmospheric pressure & O2 → hyperventilation & CO2 loss → alkalosis
b- Hypoxia also → leads to cerebral edema which could be fatal



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3) Loop Diuretics: (most Efficacious duiretics)

Agents:

- Furosemide, torsemide, ethacrynic acid, bumetanide

MOA:

↓ Na+ reabsorption in the Loop of Henle (thick ascending limb)

→ by inhibiting the “Na+/K+/2Cl- symporter”

Other effects:

1) Furosemide may dilate blood vessels

2) ↑ Ca^{2+} excretion (via ↓ Ca reabsorption; at ascending limb)

(In case of hypercalcemia → Loop diuretics + normal saline are used)

Adverse effects:

1) ↓ K+ in plasma → ↓ H+ in plasma & metabolic alkalosis

Also hypokalemia leads to:

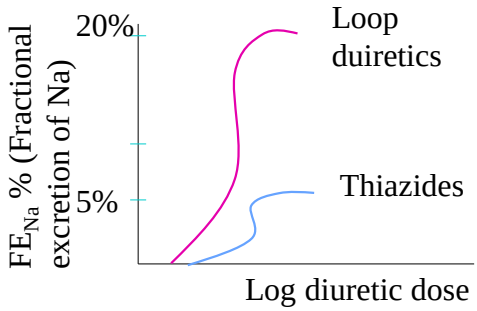
- muscle pain
- ↓ insulin release → hyperglycemia
- arrhythmia, ↑ digoxin toxicity

2) ↑ uric acid in plasma → gout

3) ↓ Na, Ca & Mg in plasma

4) ↓ blood volume

5) Ototoxicity



4) Thiazides:

Agents:

- Chlorothiazide, Hydrochlorothiazide, bendroflumethiazide
  (Chlorthalidone, Metolazone & Indapamide "Natrilix®" → thiazide-like drugs)

MOA:

↓ Na+ reabsorption in the nephron by inhibiting the Na+/CL- symporter in the distal tubule.

Other effects:

1) may dilate blood vessels
2) ↓ Ca^{2+} excretion! (by ↑ Ca reabsorption; Unlike Loop diuretics!)
   (→ used for kidney stones due to idiopathic hypercalciurea)

(Thiazides are also secreted into proximal tubules just like loop diuretics ; so both groups can cause hyper-uricemia by competing for active secretion)

Adverse Effects:

1) ↓ K+ in plasma → ↓ H+ in plasma & metabolic alkalosis

Also hypokalemia leads to:

- muscle pain
- ↓ insulin release → hyperglycemia & hyperlipidemia
- arrhythmia & ↑ digoxin toxicity

2) ↑ uric acid in plasma → gout

3) ↓ Na+ in plasma (thiazides commonly cause SIADH)

4) ↑ Ca++ (& Mg++) in plasma (→ fatigue & depression)

5) ↓ blood volume

6) Ototoxicity: (→ tinnitus & hearing loss)

(Na/K/Cl transporter is also found in the inner ear that helps formation of the endolymph fluid inside the semicircular canals)

→ Can be irreversible (ototoxicity does not happen with thiazides)

5) K-Sparing Diuretics:

A) Na+ Channel blockers: (triamterene & amiloride)

MOA:

↓ Na+ reabsorption in late distal tubule & collecting duct

(by ↓ Na channels) → inhibition of Na/K ATPase

Other effects:

↓ K+ & H+ excretion

Use:

- In combination with thiazides or loop diuretics
  → to decrease K loss caused by these diuretics

Adverse effects:

Hyperkalemia (can be life-threatening)

Risk increased in renal disease, K supplements, ACEIs, aliskiren, β blockers or NSAIDs

B) Mineralo-corticoid receptor antagonists:

Agents: Spironolactone & Eplerenone

(Eplerenone = more selective than spironolactone)

MOA:

Competitive antagonist of Aldosterone (onset is 2-3 days)

→ ↓ Na/K ATPase in late distal tubule & collecting duct

→ ↓ Na reabsorption

Other effects:

↓ K+ & H+ excretion → hyperkalemia & acidosis

Uses:

1) In combination with thiazides or loop diuretics

→ to decrease K loss caused by these diuretics

2) Treats ↑↑ plasma aldosterone in:

- 1º hyperaldosteronism (Conn's disease)
- 2º hyperaldosteronism (heart failure or cirrhosis → ↓ aldosterone metabolism)

3) ↓ androgen in women with hirsutism & alopecia

Adverse effects

1) Hyperkalemia (can be life-threatening)

- risk increased in chronic renal disease (contraindication) or with K supplements, ACEIs, aliskiren, β blockers or NSAIDs

2) Gynecomastia (esp spironolactone; less with eplerenone)

<u>Extra-renal diuretics:</u>

= Diuretics that do not act in the kidney. Include:

A) Digoxin: by increasing cardiac output → renal blood flow to kidney:

1) → ↑ GFR in kidney → decrease urine.

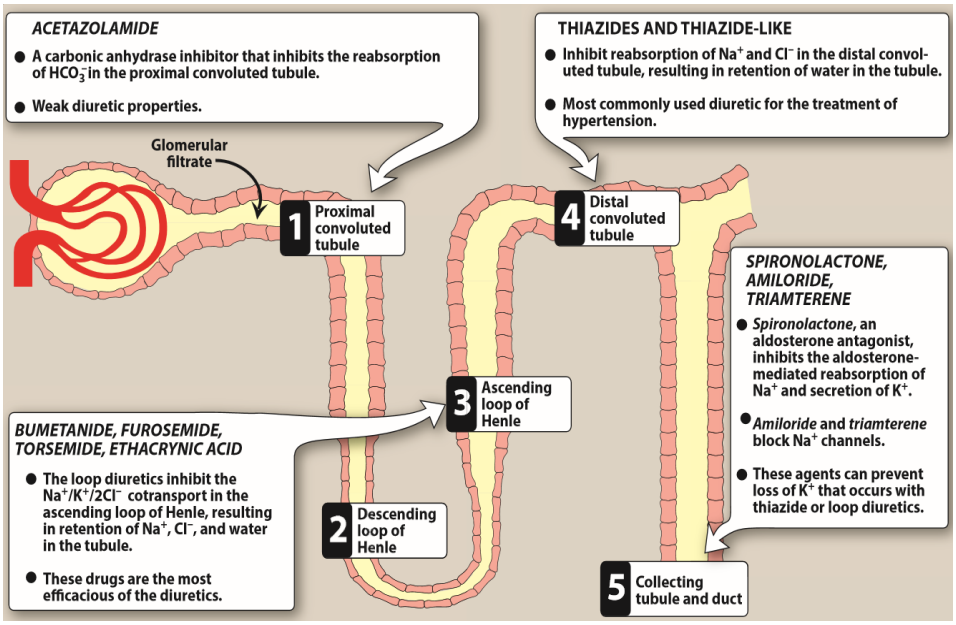
2) → ↑ BP in renal arterioles → ↓ renin secretion → ↓ Na/water retention

B) Albumin (i.v.) in case of cirrhosis with ascites (2 bottles / week)

(in cirrhosis, the liver is damaged → ↓ albumin synthesis → ↓ osmotic pressure of blood → water moves from vessels into tissues → edema)

C) ↑ water intake → ↓ ADH from the pituitary gland (also alcohol does that)

D) Alcohol → ↓ ADH release


ACETAZOLAMIDE
A carbonic anhydrase inhibitor that inhibits the reabsorption of HCO_3^- in the proximal convoluted tubule.
Weak diuretic properties.
THIAZIDES AND THIAZIDE-LIKE
Inhibit reabsorption of Na^+ and Cl^- in the distal convoluted tubule, resulting in retention of water in the tubule.
Most commonly used diuretic for the treatment of hypertension.
Glomerular filtrate
1 Proximal convoluted tubule
4 Distal convoluted tubule
SPIRONOLACTONE, AMILORIDE, TRIAMTERENE
Spironolactone, an aldosterone antagonist, inhibits the aldosterone-mediated reabsorption of Na^+ and secretion of K^+.
Amiloride and triamterene block Na^+ channels.
These agents can prevent loss of K^+ that occurs with thiazide or loop diuretics.
3 Ascending loop of Henle
BUMETANIDE, FUROSEMIDE, TORSEMIDE, ETHACRYNIC ACID
The loop diuretics inhibit the $Na^+/K^+/2Cl^-$ cotransport in the ascending loop of Henle, resulting in retention of Na^+, Cl^-, and water in the tubule.
These drugs are the most efficacious of the diuretics.
2 Descending loop of Henle
5 Collecting tubule and duct

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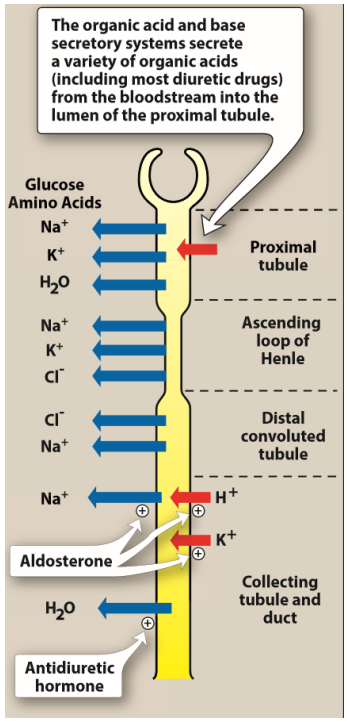

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Uses of diuretics

1) Edematous conditions:

a- Generalized edema

b- Cirrhosis with ascites

(Loop diuretics are stronger than thiazides)

c- Acute pulmonary edema:

(Thiazides are not preferred due to weaker effect, slower effect with an onset of 1-2 h & the unavailability of injectable forms. So loop diuretics are preferred)

2) Non-edematous conditions

a- Renal failure:

(Only loop diuretics are effective to treat hypertension resulting from severe renal failure)

b- Emergency & essential hypertension:

(The main action of diuretics that ↓ B.P → is the vasodilator effect)

→ Loop diuretics are better for emergency hypertension

→ Thiazides are better for chronic essential hypertension

c- Hyper-calcemia:

Acute hypercalcemia may lead to cardiac depression & standstill

→ So give a loop diuretic i.v.

d- Hyper-calciurea: (to prevent renal stones)

If the body excretes Ca in excess (idiopathic) leading to osteoporosis & Ca renal stones, give a thiazide.

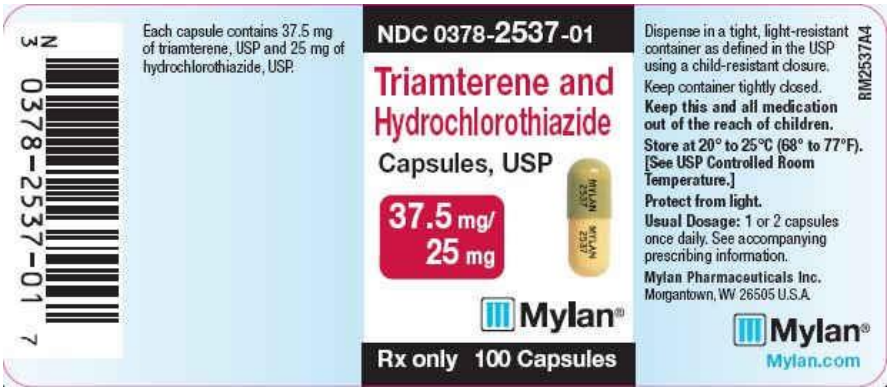
e- Nephrogenic diabetes insipidus:

ADH receptors in kidneys do not respond to ADH; give a thiazide

(MOA: unknown but may ↑ sensitivity of ADH receptors to ADH leading to paradoxical water retention!)

A) Edematous conditions	B) Non-edematous conditions (not associated with edemas)
1) Heart failure	1) Hypertension
2) Cirrhosis with ascites	2) Hypercalcemia
3) Nephrotic syndrome	3) Kidney stones due to idiopathic hypercalciurea
	4) Nephrogenic diabetes insipidus (e.g. drug-induced) → Treated paradoxically by thiazides. * Central diabetes insipidus is treated by ADH

Some Uses of Diuretics


NDC 0378-2537-01
Each capsule contains 37.5 mg of triamterene, USP and 25 mg of hydrochlorothiazide, USP.
Triamterene and Hydrochlorothiazide
Capsules, USP
37.5 mg/ 25 mg
Mylan
Rx only 100 Capsules
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Protect from light.
Usual Dosage: 1 or 2 capsules once daily. See accompanying prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Mylan
Mylan.com
RM2537A4

Note

Drugs that may cause hyperkalemia (avoid combinations):

- ACEIs
- ARBs
- K-sparing diuretics
- NSAIDs
- Heparin & low molecular heparins
- Digoxin

Other drugs affecting renal water reabsorption

A) ADH & desmopressin:

1) Arginine vasopressin = ADH in humans
2) Desmopressin (Minirin®) = 1-deamino ADH (synthetic)
   [☺ oral, longer acting, less vasoconstrictor effect than ADH]

Actions:

1) ↑ V1 receptors → vasoconstriction
2) ↑ V2 receptors → ↑ water reabsorption in the collecting duct

(↑ permeability of collecting duct to water by stimulating insertion of H2O channels into luminal membrane of the nephron epithelium)

Uses:

1) Central diabetes insipidus
2) Nocturnal enuresis

Side Effects:

1) H_2O intoxication
2) Vasoconstriction & GI effects (much less with Desmopressin)

Note:

Stages of renal failure.

- Normal kidney → GFR = 125 ml/min
- 1st stage failure → GFR = 90-120 ml/min
- 2nd stage failure → GFR = 60-90 ml/min
- 3rd stage failure → GFR = 30-60 ml/min
- 4th stage failure → GFR = 15-30 ml/min
- 5th stage (end-stage) → GFR = less than < 15 ml/min

- Thiazides can increase diuresis even if GFR reached 40 ml/min
- Loop diuretics can induce diuresis even if GFR reached 10 ml/min

B) ADH antagonists (diuretics; Vaptans)

1) Conivaptan (inj; premixed with 5% dextrose)

MOA:

V_{1A}, V_2 antagonist (block ADH receptors → ↑ water loss in urine)

Effect:

Blocking V_2 → ↑ free H2O excretion

Use: (i.v.)

* Eu-volemic or hyper-volemic hypo-natremia (↓ Na+ in blood) in hospitalized patients

(can we use regular diuretics for hypo-natremia? Why?)

Notes:

* V1 receptor activation by ADH → cause vasoconstriction in some vessels.
* V2 receptor activation by ADH → cause water retention
* These drugs are not very effective for heart failure

2) Tolvaptan: (oral)

MOA:

V_2 antagonist (selective)

Use: (like conivaptan)

- Euvolemic or hypervolemic hypo-natremia in hospitalized patients

Also, the water loss in urine could be beneficial in conditions like:

1) Heart failure (It causes water diuresis → ↓ preload & afterload)
2) Liver cirrhosis with ascites (It causes water diuresis)
3) SIADH (syndrome of inappropriate ADH)

Adverse effects of all ADH antagonists:

1) Thirst, dry mouth, polyurea
2) Correcting Na+ too rapidly → serious problems (including death)

3) Demeclocycline & lithium:

↓ ADH effect on collecting ducts in the kidney. This may cause nephrogenic Diabetes insipidus.

4) Alcohol:

↓ ADH secretion from the posterior pituitary gland → ↑ urination

Chapter 4

Anti-anginal drugs

What is Angina Pectoris?

Severe chest pain that occurs when coronary blood flow is inadequate to supply the O2 required by the heart.

(O2 supply to the heart < heart O2 demand)

What determines myocardial O2 demand & supply?

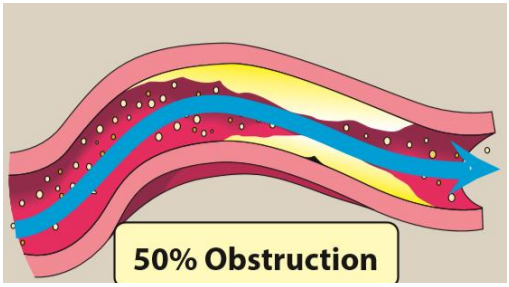
Demand	Supply
1) Wall stress (pressure, radius, thickness)	Coronary blood flow
2) Heart rate	
3) Heart Contractility	

Causes of reduced coronary heart O2 supply:

1) Coronary artery atherosclerosis
2) Coronary artery spasm

How exactly does the pain occur?

1) Insufficient blood-borne O2 supply
   → anaerobic oxidation of glucose
      → ↑ lactic acid accumulation in the myocardium
2) Lactic acid stimulates pain receptors → pain sensation



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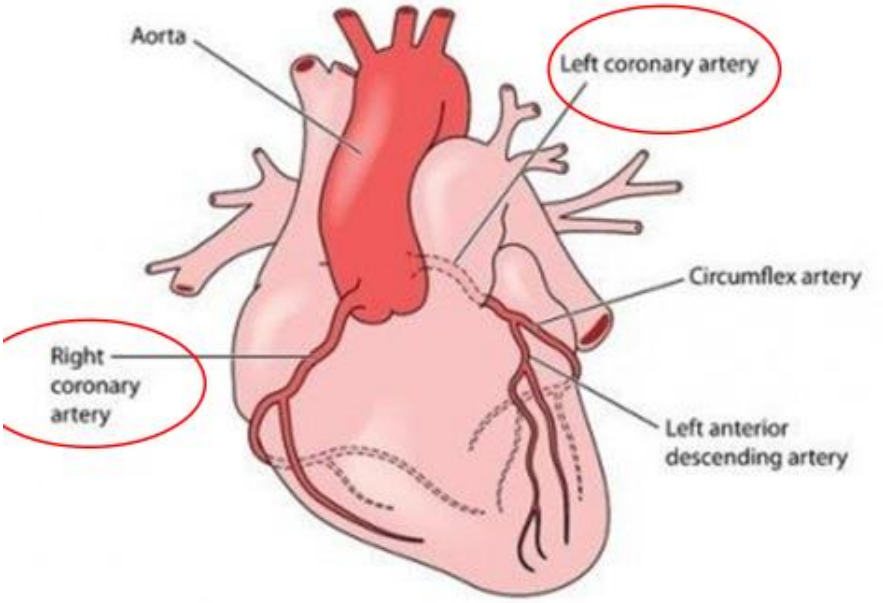


Types of Angina

☝ **Classic Angina:** (stable, effort-induced, atherosclerotic)

Pain occurs only when heart O2 requirements increases.
(e.g. during exercise)

Cause → atherosclerotic narrowing of coronary arteries.

✌ **Variant Angina** (Vasospastic; "Prinzmetal angina")

Pain may occur even at rest due to reversible coronary spasm.

Cause → may be due to ↑ α1 receptors in the coronary arteries.

🤘 **Unstable Angina**

Pain is more frequent & longer (even at rest) due to deterioration of stable angina.

Cause: → formation of mobile non-occlusive small thrombi
⇨ ↓↓ coronary blood flow even at rest.

Complications of Angina Pectoris:

May lead to myocardial infarction (MI).
(complete coronary obstruction by a clot ⇨ necrosis of part of the heart)

Approaches to treat angina:

A) ↑ coronary O2 supply by:

1) Coronary vasodilatation. (nitrates, Ca channel blockers)
2) Surgical angioplasty (stents or bypass grafts).

B) ↓ heart O2 requirements by:

1) ↓ cardiac work (↓ heart rate, ↓ contractility) ☞ by β blockers.
2) ↓ cardiac loads (↓ preload, ↓ afterload) ☞ by vasodilators.

* Angioplasty is a procedure to open narrowed or blocked blood vessels

Which drugs are used to treat angina?

1) In classic angina:

Drugs that ↓ heart O2 requirements by:

- ↓ preload or afterload (Nitrates, Ca channel blockers)
- ↓ cardiac work (β blockers)

* ↑ coronary blood flow (coronary vasodilatation) by drugs is limited by the fixed atheromatous plaques.

2) In variant angina:

Drugs ↑ coronary blood flow by coronary artery vasodilatation (Nitrates or Ca channel blockers)

Drugs used in Angina:

1) Organic Nitrates
2) Ca channel blockers
3) β blockers.

1) Organic Nitrates

* Potent Vasodilators (veins > arteries)

* 1st choice for the immediate relief of angina.

Drugs:

Nitroglycerine, isosorbide dinitrate, isosorbide-5-mononitrate

(Glyceryl trinitrate = nitroglycerin)

MOA:

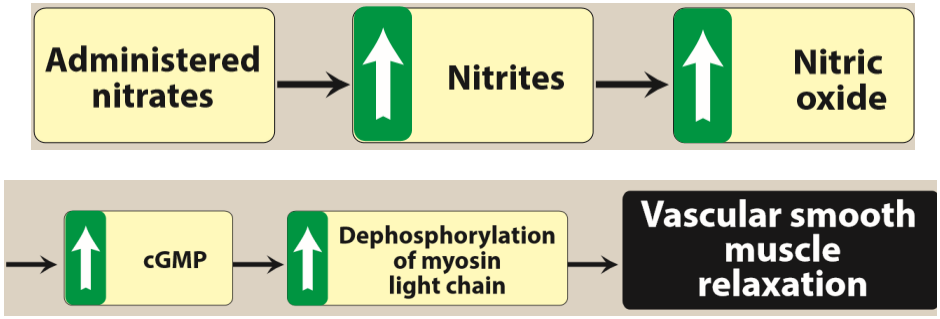
- Organic nitrates are converted inside vascular smooth muscle cells into nitrites then into nitric oxide (NO).

- ↑ NO → ↑ guanyl cyclase → ↑ cGMP ⇨ dephosphorylation of myosin light chain ⇨ vasodilation

(Myosin light chain-PO4 → Myosin light chain)

Chemical Structure:

Simple nitric & nitrous acid esters of poly-alcohols.



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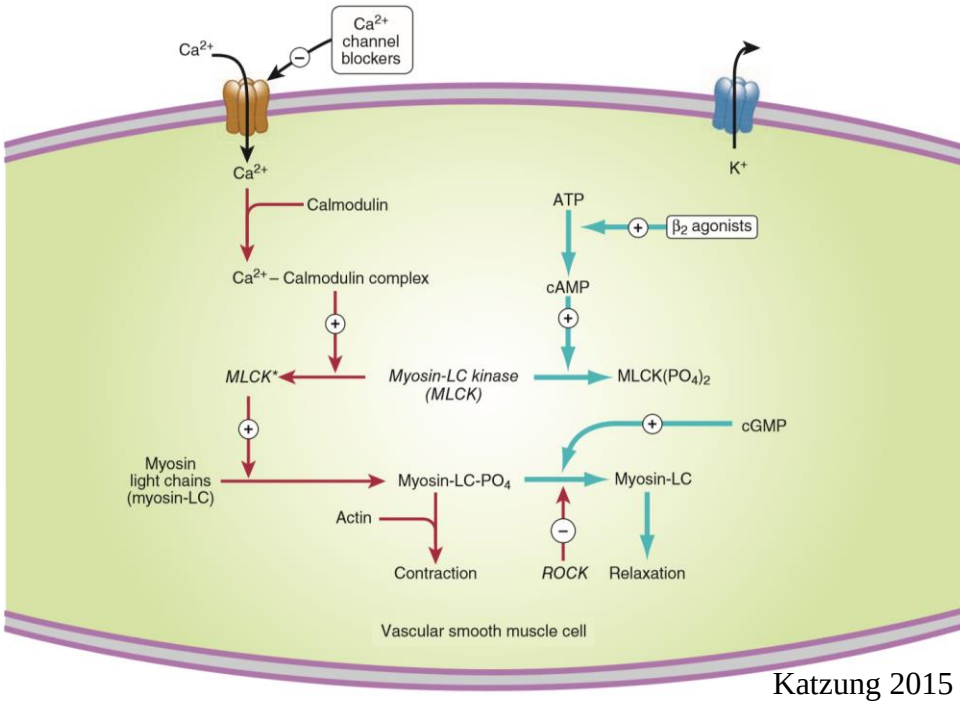
MOA of Organic Nitrates

Organic Nitrates include:

❶ Extremely volatile liquid ⇨ amyl nitrite.
❷ Moderately volatile liquid ⇨ nitroglycerin.
❸ Solids ⇨ isosorbide dinitrate..



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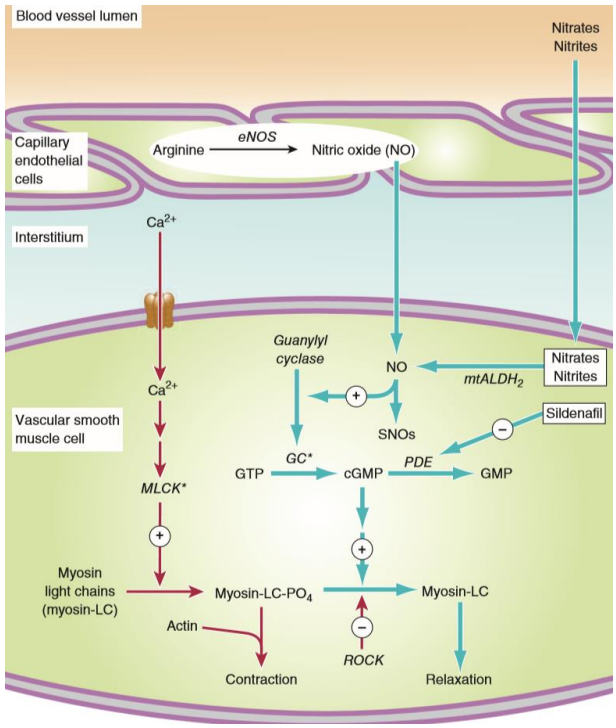

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1) Role in classical angina

- Potent vasodilators:
  - Dilate veins ⇨ ↓ intra-cardiac blood volume ⇨ ↓ preload.
  - Dilate arterioles ⇨ ↓ peripheral resistance ⇨ ↓ afterload.

- ↓ preload & ↓ afterload ⇨ ↓ heart O2 requirements.

So:

Nitrates treats effort-angina mainly by ↓ heart O2 requirements (and not by epicardial coronary vasodilatation)

2) Role in variant angina

Vasodilators of (epicardial coronary arteries) ⇨ ↓ spasm.

3) Role In unstable angina

May be due to both:

* Vasodilatation ⇨ ↓ heart O2 demand.
* ↓ platelet aggregation. (NO decrease platelet aggregation)

Routes of administration for Nitrates

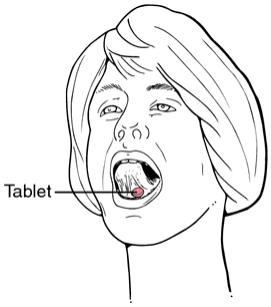
1) Sublingual:

☑ Rapid.

(onset is 1-3 min for nitroglycerin; 10 min for isosorbide dinitrate)

☒ But short in action.

- Agents ⇨ Nitroglycerin (duration = 30 min)
  ⇨ Isosorbide dinitrate (duration = 60 min)



2) Oral (sustained release):

☑ Long action (6-8 hours) but:

☹ Slow

☹ 10-20% bioavailability (heavy 1st-pass hepatic metabolism)

☹ Tolerance may develop

- Agents

⇨ Nitroglycerin, Isosorbide dinitrate, Isosorbide mononitrate.

3) Inhalation:

☑ Rapid.

Agents ⇨ Amyl nitrite (yellowish liquid in cloth-covered bulb)

highly volatile liquid ⇨ available in fragile glass ampoule can be crushed with the fingers ⇨ rapid release of inhalable vapors through the cloth covering.

4) Transdermal patches:

☑ Long acting. (1 patch/day)

But:

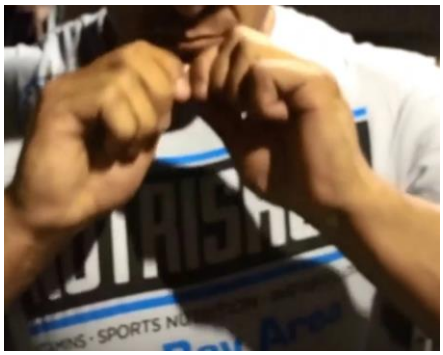
☹ Slow.

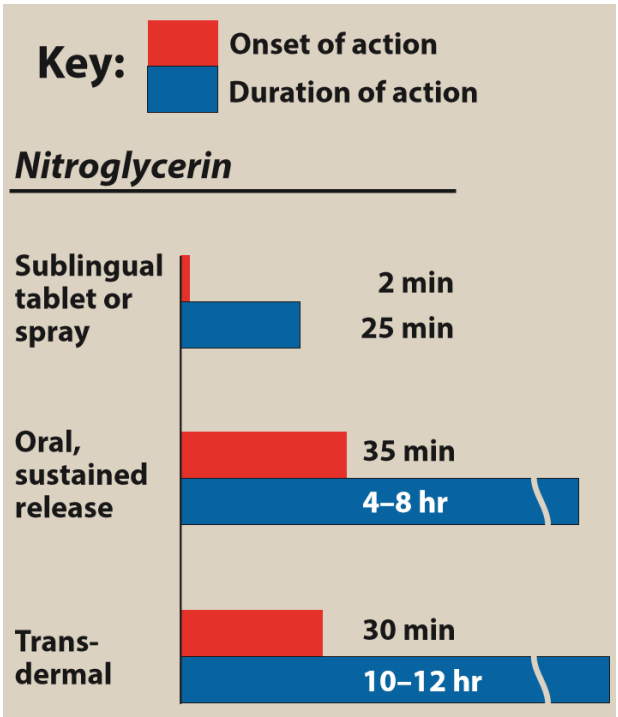
☹ Tolerance occurs.

Agents ⇨ Nitroglycerin.

5) Sublingual spray: ⇨ Nitroglycerine

How to use amyl nitrate?





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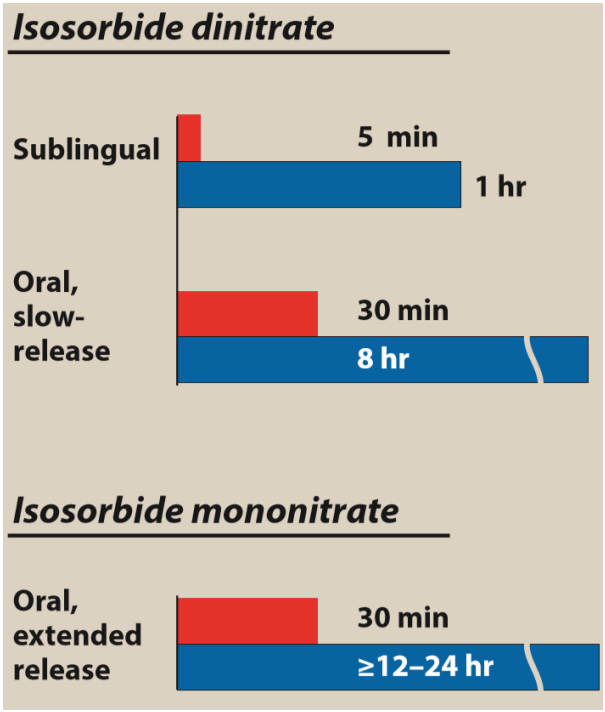

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Clinical uses

1) Nitroglycerin sublingual ⇨ Immediate relief of angina

2) Nitroglycerin i.v. ⇨ rapid but short
⇨ restricted to severe recurrent rest angina.

3) Oral, TDS (long acting) ⇨ limited use due to tolerance.

* Use of isosorbide dinitrate (sublingual or chewable) is similar to nitroglycerin.

Side effects:

1) Vasodilatation:

→ orthostatic hypotension, tachycardia, throbbing headache

2) Tolerance: rapid tolerance occurs esp. with TDS patches due to depletion of -SH stores, ↑ RAAS & ↑ intravascular fluids.

- Should we use these drugs for hypertension? Why?
- To prevent tolerance: interrupt therapy for 10 hs each day

Notes

☞ Although nitroglycerin is used in the manufacturing of dynamite, its medicinal formulations are not explosive.

☞ The conventional sublingual tablet form may lose potency when stored as a result of volatilization & adsorption to plastic surfaces so it should be kept in tightly closed glass containers. (it is not sensitive to light).

☞ Tolerance does not develop to the vasodilator action of sodium nitroprusside while it develops to nitroglycerine because enzymes which generate nitric oxide from nitroprusside are different.

2) Ca Channel blockers (esp verapamil)

M.O.A:

Block L-type Ca channels ⇨ ↓ Ca influx.

1) In smooth muscles ⇨ Vasodilatation .

2) In heart ⇨↓ contractility & heart rate ⇨ ↓ cardiac work.

a) Benefit in Angina of effort

1) ↓ cardiac work ⇨ ↓ heart O2 requirements.

2) Vasodilators:

- Veins ⇨↓ intra-cardiac blood volume ⇨ ↓ preload.
- Arterioles ⇨↓ wall tension ⇨ ↓ afterload.

↓ preload & ↓ afterload ⇨ ↓ heart O2 requirements

b) Benefit in variant angina

Vasodilators of (epicardial coronary arteries) ⇨ ↓ spasm.

(They are the most effective treatment for variant angina)

Notes:

Benefits of verapamil in the treatment of angina:

They decrease Ca entry into cells, which leads to:

1) ↓ heart work → ↓ myocardial O2 demand

2) ↓ heart rate → ↑ time of diastole (↑ coronary filling time)
→ allow blood in the coronary artery to pass to the myocardium

3) Weak coronary vasodilatation → ↑ O2 supply to the heart

4) ↓ necrosis

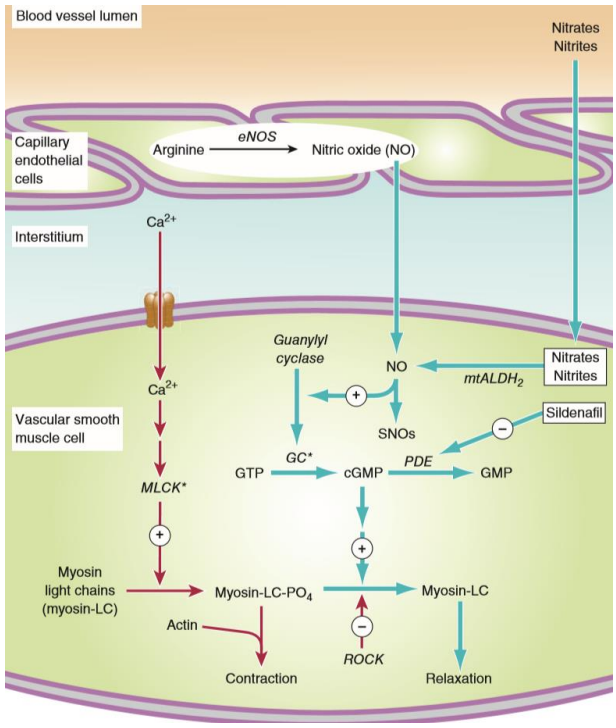
5) ↓ platelet aggregation → ↓ unstable angina or myocardial infarction

Can nifedipine be used in angina although it may cause reflex tachycardia?

Yes esp in vasospastic angina. But it has to be given in a small dose that does not cause reflex tachycardia (or in a sustained release tablet) or should be given with B blockers.

<u>* There are 2 types of MI:</u>

- STEMI = ST segment elevation MI (complete obstruction → more severe)
- Non-STEMI = (non ST segment elevation MI → less severe)



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3) β blockers

Extremely effective in the management of angina.

M.O.A:

Block β1 receptors in the heart:

⇨ ↓ contractility & heart rate ⇨ ↓ cardiac work ⇨ ↓ heart O2 requirements (demand)

Agents:

Atenolol, metoprolol, nadolol, propranolol.

Main Use:

Prevention of attacks in chronic effort angina

Disadvantage:

Not effective in variant angina.

General Principals of angina therapy

1) ↓ risk factors (smoking, hypertension, hyperlipidemia)

2) ↓ heart O2 requirements.

3) ↑ coronary blood flow.

4) To prevent myocardial infarction, use antiplatelets.

1) For Classic Angina, we use:
   → Nitrates, Ca channel blockers or β blockers.

2) For Variant angina, we use:
   → Nitrates or Ca channel blockers. (not β blockers)

3) For Unstable angina, we use:
   → Nitroglycerin + β blockers + (Antiplatelets or heparin)
   → Angioplasty is often necessary.

4) Ranolazine (Ranexa® 1x2)

- A new drug that may be added to 1st line drugs (not used alone)

MOA:

Na channels blocker → ↑ activity of Na/Ca exchangers

→ ↓ Ca concentration inside myocytes

→ ↓ heart work

→ ↓ heart O2 demand

(In angina, Na channels do not inactivate → ↑ Na entry → ↓ NA/Ca exchanger → ↑ Ca concentration inside cardiomyocytes)

Use: (not a 1st line treatment)

Add it when other drugs have failed! (it prolongs the QT interval!)

Contraindications:

1) QT-interval prolongation. (or drugs that prolong QT interval).

2) Hepatic disease

Ranolazine interactions:

1) Reduce the dose of digoxin and simvastatin because ranolazine potently inhibits CYP3A4 (↓ their metabolism).

2) With other drugs that also prolong the QT interval (macrolides, cisapride, pimozide).

3) Ranolazine must not be taken with grapefruit juice.

Notes:

- Ranolazine tabs are sustained-release so do not crush them.
- Ranolazine does not relieve acute anginal attacks.
- Ranolazine can be taken with or without food.
- Ranolazine is category C in pregnancy
- Ranolazine offers additional benefit when added to standard anti-angina drugs & possesses anti-arrhythmic properties.

5) Metabolic modulators

(pFOX inhibitors)

Trimetazidine:

↓ long-chain keto-acyl thiolase "LC-KAT" (partially)

→ ↓ fatty acid beta-oxidation (in the myocardium)

→ ↑ glucose oxidation (consumes less O2).

→ ↓ O2 demand

Although ranolazine can also work by inhibiting fatty acid beta-oxidation, its primary MOA is blocking a late Na current that facilitates Ca entry.

In the ischemic heart, metabolism shifts to fatty acid oxidation (rather than glucose oxidation) which consumes more O2.

Notes:

Coronary steal:

Caused when there is narrowing of the coronary arteries to parts of the heart and a coronary vasodilator is used "stealing" blood away from those parts of the heart.

(dilating the resistance vessels in the coronary circulation causes blood to be shunted away from the coronary vessels supplying the ischemic zone creating more ischemia)

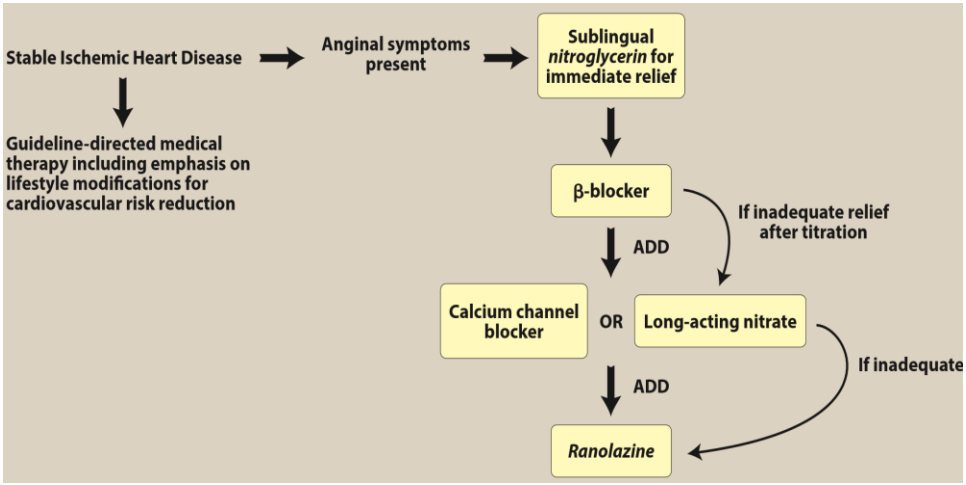
More about coronary steel:

- Caused by certain drugs like dipyridamol or nifedipine.
- The mechanism in most drug-based cardiac stress tests

(when a patient is incapable of doing physical activity, they are given a vasodilator like dipyridamol or nifedipine that produces a "cardiac steal syndrome" as a diagnostic procedure. The test result is positive if the patient's symptoms reappear or if ECG alterations are seen)

Myocardial Infarction (MI) differs from Angina:

- Angina: narrowing of coronary artery
- MI (heart attack): partial or complete obstruction of a coronary artery.



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* If a CCB is added to a β blocker, it should be a dihydropyridine

PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
100 Tablets
List No. N041.713
ISOPTIN® 80mg
VERAPAMIL HYDROCHLORIDE
80mg
ABBOTT

20 Capsules with sustained action
Iso MAK® Retard
20 mg
Isosorbide dinitrate 20 mg
Coronary therapeutic agent

Ranexa® 375 mg
Ranexa® 500 mg
Ranexa® 750 mg
Prolonged-release tablets
Ranolazine
60

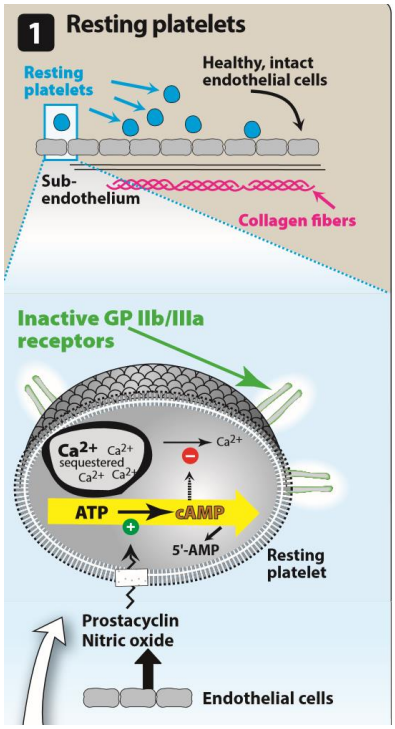
Chapter 5

Drugs for coagulation

Coagulation

- Blood can be liquid (inside blood vessels) and can also be solid (coagulates outside blood vessels)

- Blood viscosity depends on the balance between:
  - A- Natural anticoagulants. (like heparin)
    - ⇨ predominant usually.
  - B- Natural coagulation-promoting factors
    - ⇨ predominant at injury site.
- What prevents activation of coagulation factors?
  - 1) Smooth blood vessel endothelium.
  - 2) Rapid blood flow (keep platelets in the middle of the blood vessel)
- So, what activates coagulation factors?
  - 1) If platelets are in contact with a rough surface.
  - 2) Slow blood circulation.



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Hemostasis:

= spontaneous stoppage of bleeding in an injured blood vessel.

If blood coagulation is slow or fast, that may lead to either:

1) excessive bleeding or 2) thrombosis.

Steps of Hemostasis:

1) Vasospasm (via epinephrine & TXA2)

→ to decrease bleeding.

2) Platelet adhesion

→ to stop bleeding temporarily.

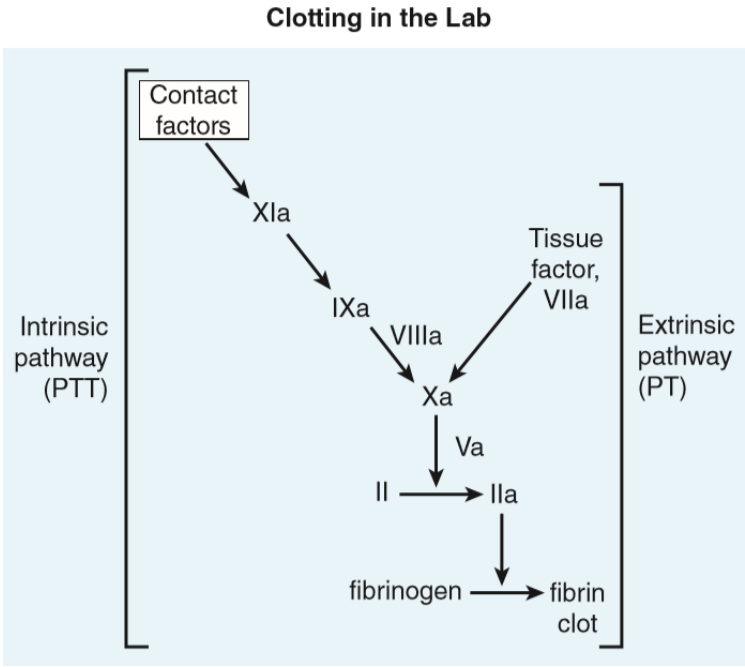
3) Thrombosis

a- The 13 coagulation factors activate one another.

b- They convert prothrombin (factor II) into thrombin (IIa)

c- Thrombin converts fibrinogen (soluble) to fibrin (insoluble)

(fibrin is factor I and maintains hemostasis by making clots stronger)



(Katzung 2015)

Remember

* Platelets secrete important substances during hemostasis:

1) TX A2 ⇨ ↑ platelet aggregation + vasoconstriction.

2) 5HT ⇨ ↑ platelet aggregation.

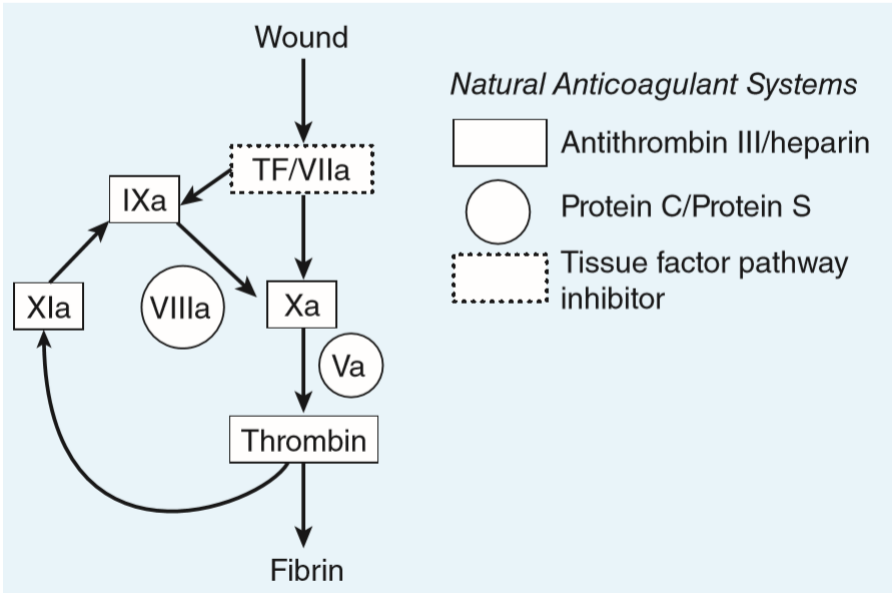
3) ADP ⇨ ↑ platelet aggregation.

4) Heparin neutralizing factor ⇨ Inhibits heparin.

5) Platelet derived growth factor ⇨ helps healing.

* The clotting cascade occurs through 2 separate pathways that interact with one another: the intrinsic and the extrinsic pathway. The extrinsic pathway is activated by external trauma that causes blood to escape from the vascular system. It is faster than the intrinsic pathway and involves factor 7 (VII).

* There are 13 coagulation factors (proteins) in plasma. They are made in the liver and help make a strong clot.



Clotting in vivo (Katzung 2015)

Component or Factor	Common Synonym	Target for the Action of:
I	Fibrinogen	
II	Prothrombin	Heparin, dabigatran (IIa); warfarin (synthesis)
III	Tissue thromboplastin	
IV	Calcium	
V	Proaccelerin	
VII	Proconvertin	Warfarin (synthesis)
VIII	Antihemophilic factor (AHF)	
IX	Christmas factor, plasma thromboplastin component (PTC)	Warfarin (synthesis)
X	Stuart-Prower factor	Heparin, rivaroxiban, apixaban, edoxaban (Xa); warfarin (synthesis)
XI	Plasma thromboplastin antecedent (PTA)	
XII	Hageman factor	
XIII	Fibrin-stabilizing factor	
Proteins C and S		Warfarin (synthesis)
Plasminogen		Thrombolytic enzymes,

(Katzung 2015)

Mechanism of blood thrombosis at injury site:

A) Collagen is exposed to blood and a rough surface is formed.

B) Platelets hit the rough surface of collagen ⇨ platelet activation.
(Collagen contain glycoproteins which bind to its GP_{IA} receptors on platelets)

C) Platelets release:

☞ TXA2, 5HT, ADP ⇨ bind to receptors on other platelets.
⇨↑ platelet aggregation & release of contents
(TXA2 & 5HT also induce vasospasm to ↓ bleeding)

☞ Heparin neutralizing factor ⇨ inhibits heparin.
(to allow activation of coagulation factors)

☞ Platelet-derived growth factor ⇨ helps healing.

D) Platelets aggregate to stop bleeding temporarily (rapid but weak)

E) Coagulation factors are activated as follows:

1) Injured tissue ⇨ releases TF (tissue factor).

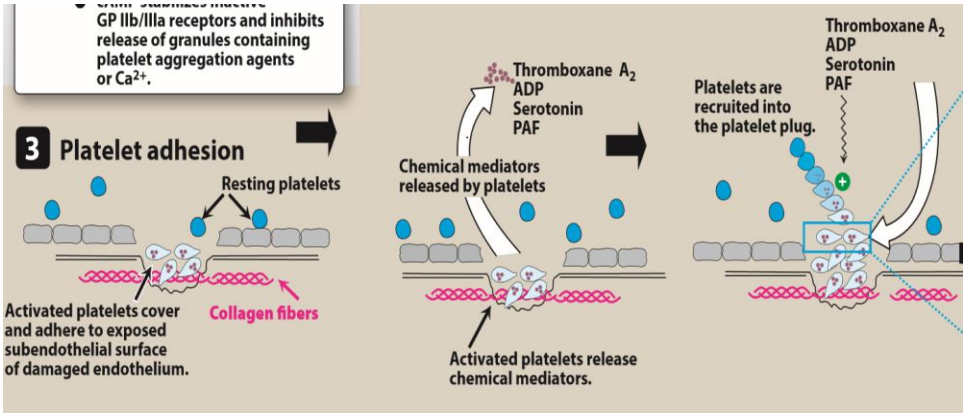
2) TF activates “factor VII” (converting it to the active form “VIIa”)
- Then “Factor VIIa” activates factor IX into the active form “IXa"
- Then “Factor IXa" activates factor X into the active form “Xa”

3) Then “Factor Xa” activates “Factor II” into its active form “IIa”
[“Factor II” = prothrombin; “Activated factor IIa” = thrombin]

4) Then “Thrombin” activates “Factor I” into the active form “Ia” which produces the initial fibrin clot.
[“Factor I” = Fibrinogen; “Activated factor Ia” = Fibrin]

5) Then “Factor XIII” stabilizes the fibrin clot.

* VIIa = activated clotting factor 7, IIa = activated factor 2, Xa = activated factor 10, IXa = activated factor 11, XIa = activated factor 9, Ia = active factor 1.



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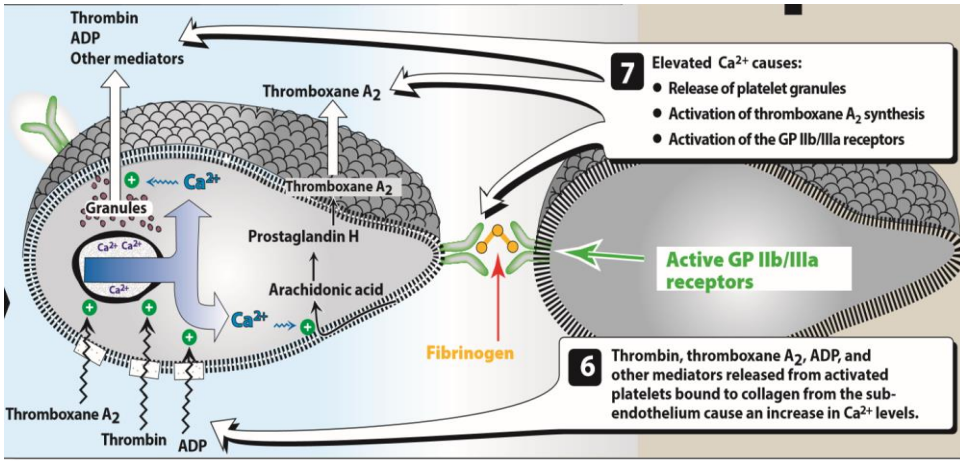

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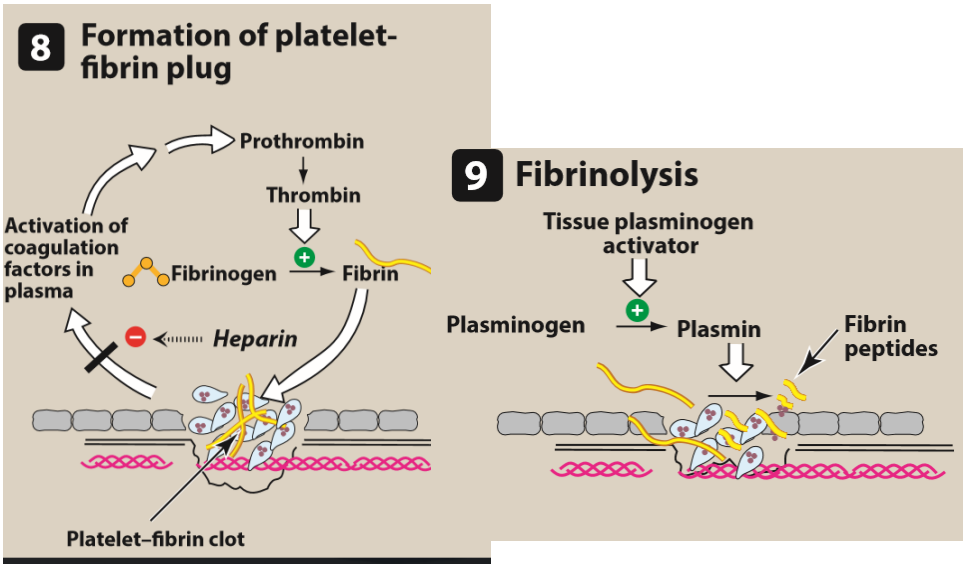

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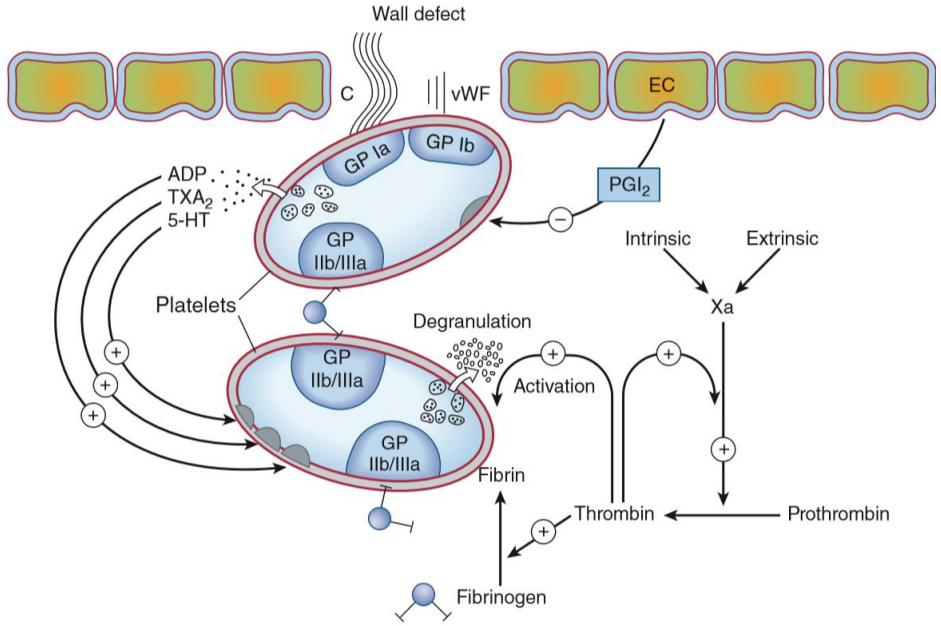
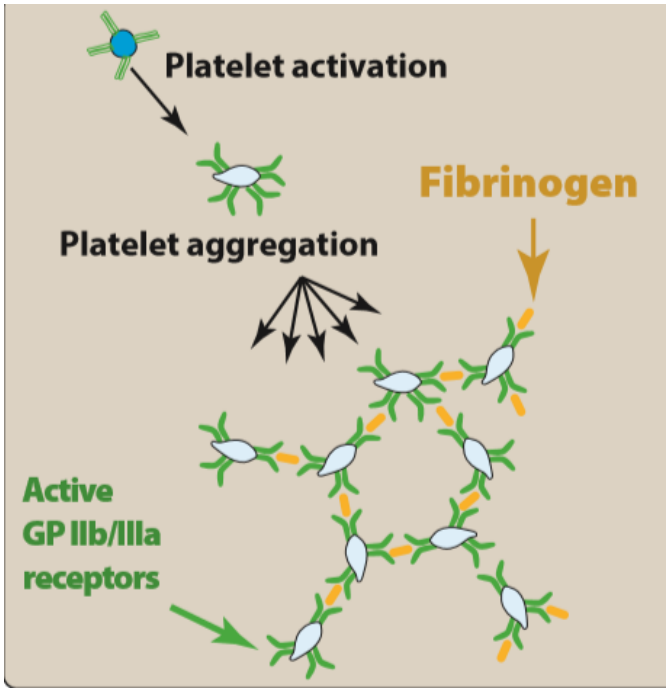


Coagulation upon injury (Katzung 2015)



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Notes:

☑ Factor XIII = A trans-aminase that cross-links the fibrin polymer.

☑ Coagulation factors are either:

- serine proteases (e.g. factors 2, 7, 9, 10, 12) or
- carriers for other coagulation factors (e.g. factors 5, 8, 11)

☑ Platelets induce rapid but weak stoppage of bleeding
Coagulation factors induce slow but strong stoppage of bleeding

☑ Coagulation factors are activated by proteolytic reactions.

☑ Ca^{2+} is one of the coagulation factors (coagulation factor IV).

.

When does blood coagulates to form clots?

A) Physiological

⇨ wounds. (collagen has a rough surface).

B) Pathological

- Atherosclerosis.

(when endothelium ruptures after years of increased cholesterol deposition in the walls of blood vessels, the collagen gets exposed and a rough surface is formed on the endothelium of b. vessels)

- Long recumbence in bed or heart failure.
  (slow blood circulation)
- ↑ coagulation factors.
  (due to pregnancy, contraceptive use or obesity)

Classification of drugs inhibiting thrombosis

1) Antiplatelets (e.g. Aspirin)

They inhibit platelet aggregation.

- Used to ↓ occurrence of thrombus. (prophylaxis)
- Cause less hemorrhage side effects (than anticoagulants)

2) Anticoagulants (e.g. heparin & warfarin)

They inhibit coagulation factors.

- Used to ↓ recurrence or propagation of thrombus. (prophylaxis)
- Cause more hemorrhage side effects. (than antiplatelets)

3) Thrombolytics (e.g. streptokinase)

They ↑ plasmin.

- Used to dissolve the formed thrombus. (treatment)
- Cause even more hemorrhage side effects. (than anticoagulants)

(thrombolytics cause more hemorrhage side effects because they dissolve useful clots at injury sites e.g. at skin, GIT…etc)

Notes:

* Main natural Anticoagulants:
    1) PG I_2 (= prostacyclin; released from vascular endothelium).
    2) Heparin (activates anti-thrombin).
    3) Anti-thrombin (↓ thrombin & other coagulation factors).

* The main natural thrombolytic in the body is “plasmin”.

Antiplatelet drugs

Use:

Prophylaxis against thrombosis occurrence in patients with high risk of thrombosis. (hypertensive, atherosclerosis, old-aged)

Receptors on platelets

❶ TX_{A2}, $5HT_2$, ADP:

❷ GP Ia: activated normally by collagen.

❸ GP II_b/III_a: activated normally by fibrinogen & fibronectin.

* All these receptors are linked to Gq that stimulates phospholipase C then: Phospho-inositol-bisphosphate ➞ Inositol-tri-phosphate + di-acyl-glycerol “DAG”. (DAG ➞ ↑ Ca from endoplasmic reticulum ➞ release of platelets contents).

* Also A1 receptor on platelets ⇨ ↑ Gi ⇨ ↓ adenyl cyclase ⇨ ↓ cAMP ⇨ Ca release ⇨ ↑ platelet aggregation.

* The average life span of circulating platelets is 8 to 9 days.

a) Phospho-di-esterase (PDE) inhibitors

Remember that inside platelets, ATP is coverted into cAMP. cAMP is beneficial because it prevents Ca release from the endoplasmic reticulum inside platelets → ↓ TX A2, ADP , 5HT release from platelets → ↓ platelet aggregation.

cAMP is degraded by phospho-di-esterase into "inactive" AMP.

M.O.A of PDE inhibitors:

↓ phosphodiesterase III & V

⇨ ↑ cAMP ⇨ ↓ TX A2, ADP & 5HT ⇨ ↓ platelet aggregation.

Agents:

- Methyl xanthines: (Non-specific PDE inhibitor; also block A1 receptors)

E.g. pentoxyphylline.

Used only for intermittent claudication (a muscle pain resulting from peripheral artery disease)

- Dipyridamol (specific PDE III inhibitor, Persantin® 75 mg tabs)

MOA:

↓ phosphodiesterase III specifically in platelets & blood vessels
→ ↓ platelet aggregation & ↑ vasodilation

- Usually used with aspirin to prevent stroke
- ☹ variable bioavailability & causes postural hypotension
  → less commonly used

- Cilostazol: (specific PDE III inhibitor)

MOA:

Same as dipyridamol but more commonly used because it is:

☺ Oral

☺ Better than pentoxyphyllin for intermittent claudication

☺ ↓ triglycerides & ↑ HDL

b) ↓ arachidonic acid pathway (Aspirin)

Arachidonic acid pathway:

1) Phospholipids → Arachidonic acid (by phospholipase A2)
2) Arachidonic acid → Endoperoxide (by COX I or II)
3) Endoperoxide → different PGs (by PG synthetase)

In vessels endothelium:

COXII converts endoperoxide into PG I2 (prostacyclin) which:

⇨ ↓ platelet aggregation

In platelets:

COX I converts endoperoxide into TX A2 (thromboxane A2)

⇨ ↑ platelet aggregation

Agents:

Acetyl salicylic acid (Aspirin)

M.O.A:

Low dose ⇨ long inhibition of COXI in platelets ⇨ ↓↓↓ TX A_2

⇨ short inhibition of COXII in endothelium ⇨ ↓ PG I_2

⇨ PG I2 >>> TX A2 ⇨ ↓ platelet aggregation.

Dose:

Small dose (e.g. 75 mg once or twice daily).

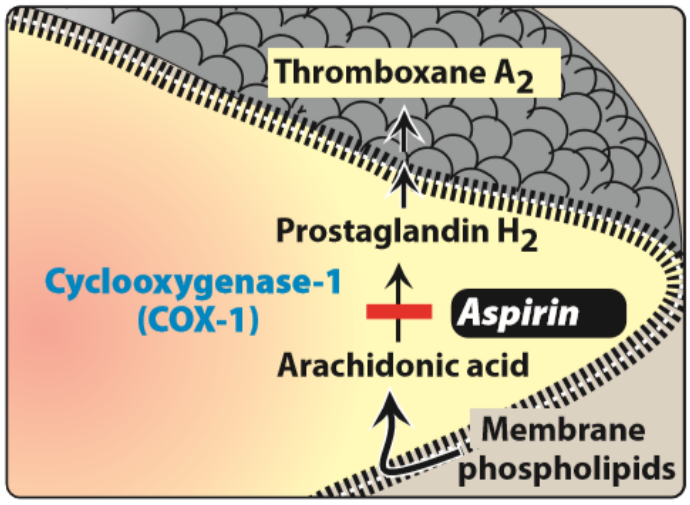
Clinical use:

Commonly used to prevent myocardial infarction

Aspirin high dose is not used as an antiplatelets due to:

1) ↓↓↓↓↓ TX A2 = ↓↓↓↓↓ PG I2. (no antiplatelet effect)
2) more hemorrhage due to more TX A2 inhibition. (more side effects)

- Other salicylates cause reversible inhibition of COX (not used)
- Aspirin causes irreversible acetylation of COX (preferred)



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c) ↓ ADP-induced platelet aggregation

Agents:

* Ticlopidine (Ticlid® 250 mg tabs)
* Clopidogrel (Plavix® 75 mg tabs; other drugs are prasugrel & ticagrelor)

☺ Clopidogrel has less side effects than ticlopidine (neutropenia)

☺ All 1X1 (except ticagrelor 1X2)

MOA:

Block P2Y12 receptors of ADP (on platelets)

Notes:

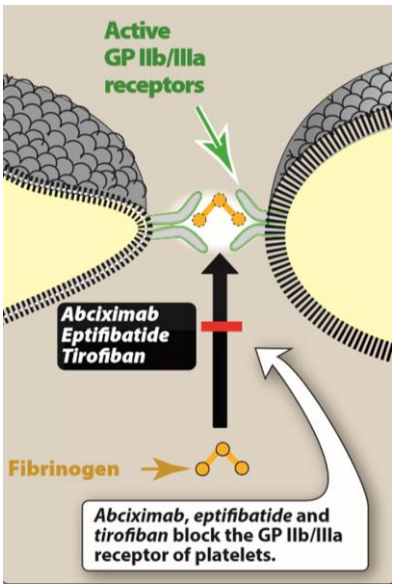
* These drugs are prodrugs.
  (Do not give with certain CYP450 inhibitors like omeprazol)
* These drugs are slow (5 days to reach effective concentrations)

d) ↓ GPIIb/GPIIIa receptors

Agents: (i.v. infusion)

- Abcimiximab
- Eptifibatide & Tirofiban

(Their use decreased after development of P2Y12 inhibitors)



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Anticoagulants

A) Parenteral Anticoagulants (e.g. heparin)

M.O.A:

↓ activity of coagulation factors in blood ⇨ rapid.

Agents:

☑ Heparin & dermatan. (Indirect inhibitors of coagulation factors)

☑ Hirudin. (Direct inhibitors of coagulation factors)

B) Oral Anticoagulants (e.g. warfarin)

M.O.A:

↓ synthesis of coagulation factors in liver ⇨ slow.

Agents:

☑ Warfarin & dicumarol.

A) Parenteral anticoagulants

1) Heparin (Un-fractionated Heparin or high-molecular-weight)

A glycos-amino-glycan (muco-polysaccharide) containing –vely charged sulfate groups. (naturally secreted from mast cells)

Source: From animals. (from porcine intestinal mucosa or bovine lung)

M.O.A:

↑ antithrombin III ⇨ ↓ active "serine protease" coagulation factors (esp. factors **2** , 9 , **10** , 11 , 12).

Pharmacokinetics:

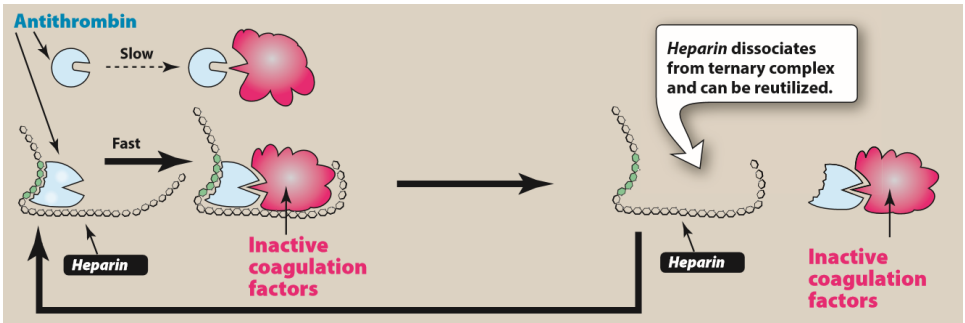
Polar ⇨ not absorbed orally. (i.v. ⇨ faster effect or s.c. ⇨ slower)

⇨ limited distribution. (safe during pregnancy or lactation)

⇨ rapid metabolism. (t1/2 = 1-2 hr; infusion or frequent inj)

* If administered i.m. ⇨ hemorrhage ⇨ hematoma.

* Metabolism is rapid by "heparin neutralizing factor".



How heparin inactivates coagulation factors (Lippincott 2015)

* Low concentrations of heparin selectively interfere with the Intrinsic pathway of coagulation.

Preparations:

1) Heparin Na

2) Heparin lithium or calcium

for patients with hypertension or renal diseases.

Side effects:

☹ Hemorrhage. (main side effect)

☹ ↑ Lipoprotein lipase ⇨ ↑ fatty acids in blood.

☹ ↑ hair metabolizing enzymes ⇨ hair loss.

☹ ↑ bone metabolizing enzymes ⇨ osteoporosis (rare)

☹ Heparin-induced thrombocytopenia (HIT)
(changes shape of platelets → immune-mediated attack → ↓ platelets)

☹ Allergic thrombosis (may result from HIT)

☹ Hyperkalemia (suppresses aldosterone)

Antidote for heparin: Protamine slow i.v. infusion.
(a basic +vely charged compound)

b) Low molecular weight heparins (LMWHs)

- Synthetic drugs (produced by enzymatic depolymerization of heparin)
- Inhibits clotting factor X (10) more selectively
- Less effect & less side effects compared to heparin

☺ Advantages:

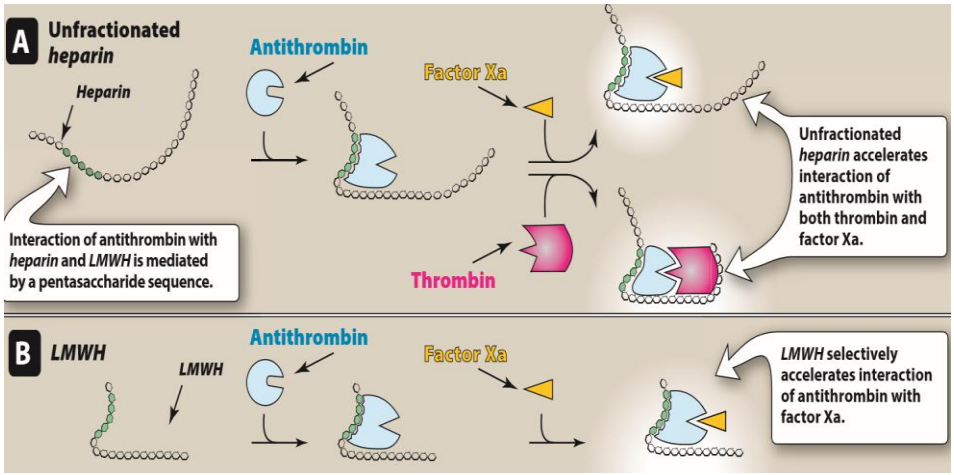
1) Prolonged effect 2) Less bleeding side effects.
3) Less need for monitoring (compared to heparin)

☹ Disadvantages:

1) delayed effect 2) Less potent.

Agents:

1) Enoxaparin. (Clexane®; s.c. 1×2)
(the most commonly used among LMWHs esp after orthopedic surgery)
2) Dalteparin (s.c. 1×1)
3) Tinzaparin (s.c. 1x1)
*) Fondaparinux (= synthetic penta-saccharide)


A Unfractionated heparin
Heparin
Antithrombin
Factor Xa
Thrombin
Interaction of antithrombin with heparin and LMWH is mediated by a pentasaccharide sequence.
Unfractionated heparin accelerates interaction of antithrombin with both thrombin and factor Xa.
B LMWH
LMWH
Antithrombin
Factor Xa
LMWH selectively accelerates interaction of antithrombin with factor Xa.

MOA of both heparin & low molecular weight heparin (Lippincott 2015)

* Heparin cream is available "Contractubex®" and may help in fresh scar healing by enhancing blood flow.

c) Dermatan: (rarely used)

- Found mostly in the skin (but also in other tissues)
- An i.v. drug used only in cases of "heparin allergy".
- M.O.A → ↑ antithrombin II.

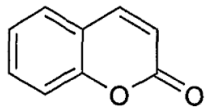
d) Hirudin:

- An i.v. drug extracted from saliva of a leech (Hirudu medicinalis).
- Lepirudin = recombinant hirudin but differs in 1 amino acid
- Bivalirudin = synthetic congener (prodrug) of hirudin

* An example of a typical anticoagulation therapy:
  1) 10 days ⇨ Heparin i.v.
  2) 5 days ⇨ Heparin i.v. & Warfarin oral
  3) 6 weeks - 6 months or longer ⇨ Warfarin oral

* Once stroke has occurred, no antiplatelet drug alters the course of neurological or other complications. However, they do reduce the occurrence of stroke and transient ischemic attacks.

B) Oral anticoagulants



coumarin

1) Warfarin:

A coumarine derivative. (Caumadin® 1, 2 , 3….10 mg)

Properties:

☑ Fat soluble

⇨ oral.

⇨ wide distribution. (contraindicated in pregnancy & lactation)

⇨ slow metabolism & excretion. (1X1)

☑ Slow onset (does not affect the already formed clotting factors; marked effect appears after 3-5 days)

M.O.A:

↓ "Vit K epoxide reductase" in the liver:

→ ↓ synthesis of clotting factors 2, 7, 9, 10 (in the liver).

(inhibits re-activation of vit K1)

Dose:

5-10 mg daily usually at 5 or 6 pm. (Then the dose is assessed by PT)

Side effects:

1) Hemorrhages.

2) Venous thrombosis.

(↓ "protein C" synthesis ⇨ thrombosis ⇨ necrosis of skin... etc)

Notes:

- Warfarin is given daily at 5 or 6 pm to allow same-day dose changes by a prior visit to the doctor earlier in the same day.
- Dicumarol is rarely used due to ☺ poor absorption ☹ GIT side effects.
- Dosing of oral anticoagulants is assessed by PT (by calculating INR) (prothrombin time = 12 sec; measures speed of the extrinsic pathway)
- Dosing of heparin is assessed by aPTT ("activated partial thromboplastin time" = 30-50 sec normally; it measures speed of the intrinsic pathway)
- PT (INR) & aPTT with therapy should be 1½ - 2½ fold longer than normal.

2) Dabigatran (oral)

MOA: A direct factor IIa (thrombin) inhibitor

Advantages:

☺ Oral, effective & has predictable pharmacokinetics

Dabigatran vs warfarin:

☺ No need for routine monitoring
[for the international normalized ratio (INR)]

☺ ↓ drug interactions as compared to warfarin

☹ No antidote available

☹ More expensive

Uses:

- Atrial fibrillation
- An alternative to enoxaparin before orthopedic surgery

* Rivaroxaban & apixaban → similar to Dabigatran but inhibit factor Xa

Heparin	Warfarin
Parenteral	Oral
GlycosoAminoGlycan (GAG)	Coumarine derivative
From animals	Synthetic
(-ve) charged acid ⇨ water soluble	Uncharged ⇨ fat soluble
Unabsorbable from GIT	Absorbable.
Does not pass BBB or placenta	Passes BBB or placenta
Rapid & Short (if i.v.) Slow & prolonged (if s.c.)	Slow & prolonged.(onset = 8-12 hrs)
Safe (children, pregnancy, lactation)	Not safe in pregnancy (hemorrhage, abnormal bone formation)
For initial therapy	For maintenance therapy
Antidote = protamine	Antidote = Vit K (acts within 1 day so give fresh frozen plasma with vit K)
Monitored by measuring aPTT	Monitored by measuring PT (by calculating INR)

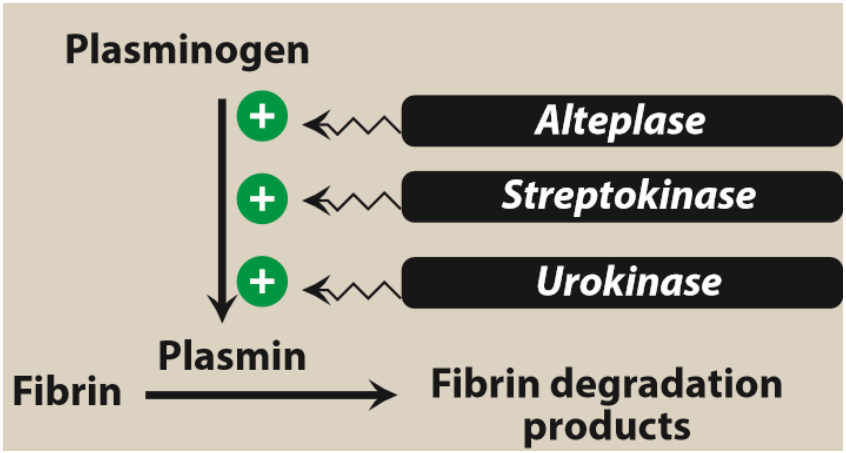
Thrombolytics

Thrombolytics (or Fibrinolytics) rapidly dissolve thrombi
→ prevent ischemia or tissue death if administered early.

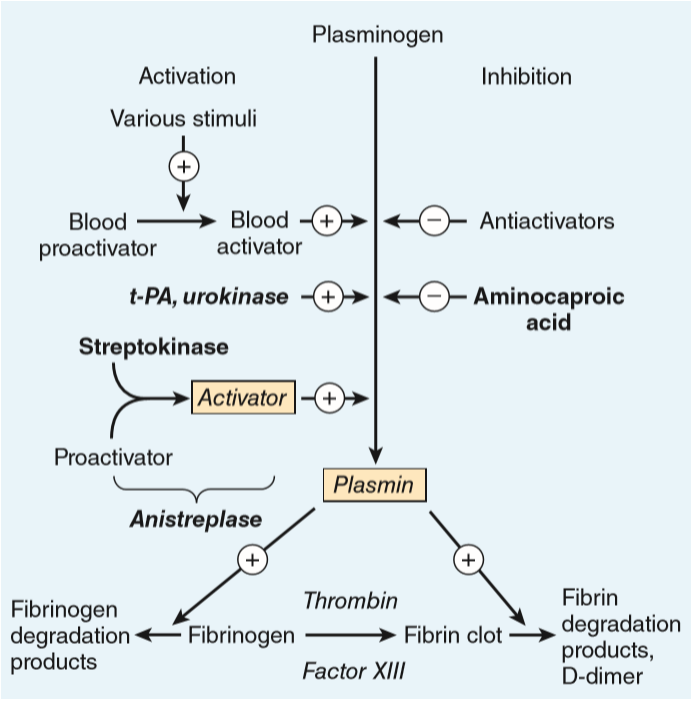
They should be given within 5 minutes in cerebral thrombosis.
They should be given within 6 hrs in myocardial infarction.
They should be given within 24 hrs in occlusion of peripheral vessels.

M.O.A:
- Activate “plasminogen” into the active form “plasmin”.
- Then “plasmin” dissolves thrombi.

Physiologically, thrombolysis occurs as follows:
1) Plasminogen → Plasmin (by tissue plasminogen activator t-PA)
2) Fibrin is broken down into fibrin fragments (by plasmin)



MOA of thrombolytics (Lippincott 2015)



(Katzung 2015)

Agents (proteolytic enzymes):

1) Non-specific

- Dissolve thrombi & other plasma clotting factors (factor V & VII) ⇨ ↑ bleeding side effects.
- Drugs: streptokinase & urokinase.

2) Relatively specific:

- Drugs: acylated plasminogen + streptokinase

3) Specific:

- Dissolve thrombi only ⇨ least bleeding side effects
- Drugs: alteplase (recombinant t-PA)

Main indications:

1) Myocardial infarction (MI)
2) Pulmonary emboli (PE)
3) Deep Venous thrombosis (DVT)

	Streptokinase	Urokinase	Acyl plasminogen + Streptokinase	t-PAs
Specificity	**Not specific**	**Not specific**	**partially specific**	**specific**
Potency	**4**	**3**	**3**	**1**
Allergy	**yes**	**no**	**yes**	**No**
Hemorrhages	**yes**	**yes**	**few**	**No**

1) Streptokinase (i.v.)

Source:

A bacterial protein isolated from β-hemolytic Streptococci.

M.O.A:

Proteolytic activation of Plasminogen (plasminogen → Plasmin).

Side effects:

1) Bleeding. (due to proteolytic lysis of clotting factors in plasma)
2) Allergy. (a foreign compound!)

Clinical use:

Recent myocardial infarction.
(within 6 hrs; rarely used now due to side effects)

* A patient suffering from hematemesis following streptokinase can be controlled by giving “epsilon aminocaproic acid”.

2) Urokinase (i.v.)

Source:

Human enzyme synthesized by kidney and excreted in urine.
(collected from cultures of human kidney cells)

Advantage:

No allergy.

Disadvantage:

less potent & not fibrin-specific → less used currently

Preparations:

Vials.

3) Relative-specific thrombolytics

= Acylated plasminogen + small dose of Streptokinase.

M.O.A:

Acylated plasminogen → plasminogen. (slowly)

Plasminogen → Plasmin by streptokinase

Advantages:

1) long action.
2) less bleeding side effects.
3) i.v. bolus.

♪ With thrombolytics add:

1) Corticosteroides to prevent allergy.
2) β blockers to decrease cardiac work.

4) Specific thrombolytics

↑ plasminogen (that is bound to fibrin) at site of thrombus only
→ less bleeding side effects. (so we call them "fibrin-specific")

Agents: (i.v. bolus except alteplase: bolus then infusion "short t1/2")

1) Alteplase = recombinant t-PA ⇨ i.v. infusion over 1 h (short t1/2)
2) Reteplase = mutant t-PA ⇨ i.v. bolus
   (shorter so cheaper but less fibrin selective)
3) Tenecteplase = mutant t-PA ⇨ i.v. bolus.
   (slightly more fibrin selective)
4) Anistreplase = mutant t-PA ⇨ i.v. bolus.

♪ To treat bleeding of thrombolytics, give tranexamic or aminocaproic acid.

♪ After thrombolysis, anticoagulants (heparin then warfarin) should be given to prevent recurrence.

♪ Streptokinase & urokinase activate fibrin-bound plasminogen at the thrombus site but also activates circulating plasminogen → more bleeding side effects.

Plavix
75 mg film-coated tablet Clopidogrel
28 film-coated tablets

98 tabletter
Pletal 100 mg
CILOSTAZOL

Marevan™
Warfarin Sodium 3 mg
100 tablets
GlaxoSmithKline
ماريفان
١٠٠ قرص
GlaxoSmithKline

NDC 25021-400-01
HEPARIN
Sodium Injection, USP
1,000
USP units per mL
1 mL Multi-Dose Vial

CLEXANE®
4000anti-Xa IU / 0.4 ml
(Enoxaparin sodium)
Injectable solution

NDC 50242-041-64
List No.: 1357
US License No.: 1048
cathflo® activase®
(ALTEPLASE) 2 mg
For Use in Central Venous Access Devices
℞ only
KEEP REFRIGERATED
Genentech
NDC 50242-041-63
Cathflo® Activase®
(Alteplase)

Dabigat
Pradaxa
75 mg
Dabigat
Pradaxa
110 mg
30 capsules
Dabigatran etexilate
Pradaxa®
150 mg
Capsule
Boehringer
Ingelheim

Chapter 6

Hemostatic Drugs

Hemostatic Drugs (to stop bleeding)

A) Local hemostatics (styptics)

1) Physical methods

- by pressing or by using “cold packs”.

- Ice packs can help minimize swelling around the injury, reduce bleeding into the tissues, and reduce muscle spasm and pain.

- You can also put ice cubes in a plastic bag or wet tea towel.

- Apply cold packs for periods of up to 20 minutes every two to four hours over a period of 24-72 hrs.

- E.g. for ankle sprains or after teeth removal (on the cheek)

- You can also use cold running water to both clean the wound and to cause vasoconstriction.

- Heating pads (even a hot wet towel) should be used for chronic conditions to help relax and loosen tissues and to stimulate blood flow.

2) Tannins (tea bag in a gauze)

- They precipitate clotting factors.

3) Local vasoconstrictors

- e.g. adrenalin & phenylephrine (usually as packs).

4) Thrombin

- Powder or solution.

5) Fibrin

- Powder (esp. in some surgeries; called “fibrin glue” or “fibrin sealant”; contains fibrinogen + thrombin)

An ice pack & a heating pad

B) Systemic hemostatics

1) Vit C

- For bleeding resulting from vit C deficiency. (e.g. scurvy)

2) Concentrated clotting factors (i.v.)

- Concentrated human plasma fractions
- Treat severe hemophilia.

3) Desmopressin (synthetic form of arginine vasopressin)

- ↑ activity of 8th factor ⇨ treats mild hemophilia. (oral)

4) Antiplasmins (fibrinolysis inhibitors; t-PA inhibitors)

- Competitive inhibitors of t-PA ⇨ ↓ plasmin formation.
- Agents:
  - * Aminocaproic acid (oral or i.v.; antidote for fibrinolytics)
  - * Tranexamic acid (oral or i.v.)
  - * Aprotinine (i.v.; withdrawn from the market then re-introduced)

5) Vitamin K (oral, inj)

- Activates synthesis of clotting factors 2, 7, 9, 10.

Vit K1 (phytomenadione): found in leafy vegetables

Vit K2 (menaquinone): found in animals.

Vit K3 (menadione): synthetic.

- Vit K1 is the principal form used (oral or inj)
- Vit. K3 is water-soluble ⇨ rapid ⇨ used only for warfarin toxicity
- ☹ Vit K needs 24 hrs to synthesize enough clotting factors and show effect.

* Vit K1 should be given oral or s.c. inj. Only if necessary, i.m. or i.v. injection may be used but the i.v. inj must be very slow (not exceed 1 mg/min). Otherwise, anaphylactic shock may occur.

6) Etamcylate (Dicynone®: oral, i.v., i.m.)

↑ platelet adhesion & supports capillary wall.

Main inherited bleeding disorders:

1) Hemophilia A (Classic hemophilia)

- Lack of coagulation factor 8 (anti-hemophilic factor)

2) Hemophilia B (Christmas hemophilia)

- Lack of coagulation factor 9 (Christmas factor)
- Hemophilia is controlled by a sex-linked gene (only occurs in males)

3) Hemophilia C

- Lack of coagulation factor 11.

4) Von Willebrand's disease

- Lack of Von willebrand factor.

(A glycoprotein that stabilizes f8 & necessary for normal platelet function. It binds to GP Ib receptor on platelets)

There are also other diseases in which other factors are deficient (e.g. factors 1, 2, 5, 7, 10, 12, 13)

Note:

Cases requiring vit K supplements:

1) For those who cannot get enough vitamin K:
   A- ICU hospitalized patients.
      (due to parenteral nutrition "no food intake" & recent surgery)
   B- Premature babies
   C- Severe liver failure

2) Multiple antibiotic therapy.
   (antibiotics kill normal flora that synthesize vit K2)

(Premature babies have immature livers → ↓ synthesis of clotting factors → peri-ventricular hemorrhage. So vit K helps to activate clotting factors. Breast milk is also low in vit K).

Konakion® MM 2 mg
Wirkstoff: Phytomenadion
(Vitamin K1)
2 mg oral/i.m./i.v.
5 Ampullen zu je 0,2 ml
Lösung N1
5 Dispenser
Roche

Dicynone® 250 mg tablete
ETAMSILAT
30 tableta
lek

FOR TOPICAL USE ONLY
DO NOT INJECT
THROMBIN,
TOPICAL
(BOVINE ORIGIN) U.S.P.
THROMBIN-JMI®
5,000 International Units
King Pharmaceuticals
STERILE
FOR TOPICAL USE ONLY
DO NOT INJECT
THROMBIN,
TOPICAL
(BOVINE ORIGIN) U.S.P.
THROMBIN-JMI®
20,000 International Units
King Pharmaceuticals
STERILE

TISSEEL
[Fibrin Sealant]
For Topical Use Only

Chapter 7

Drugs for Anemia

Drugs for Anemia

Hematopioesis:

The production of RBCS, WBCs, platelets from undifferentiated stem cells in the bone marrow.

(200 billion blood cells are formed per day, 2-3 million RBCs formed / sec)

Anemia:

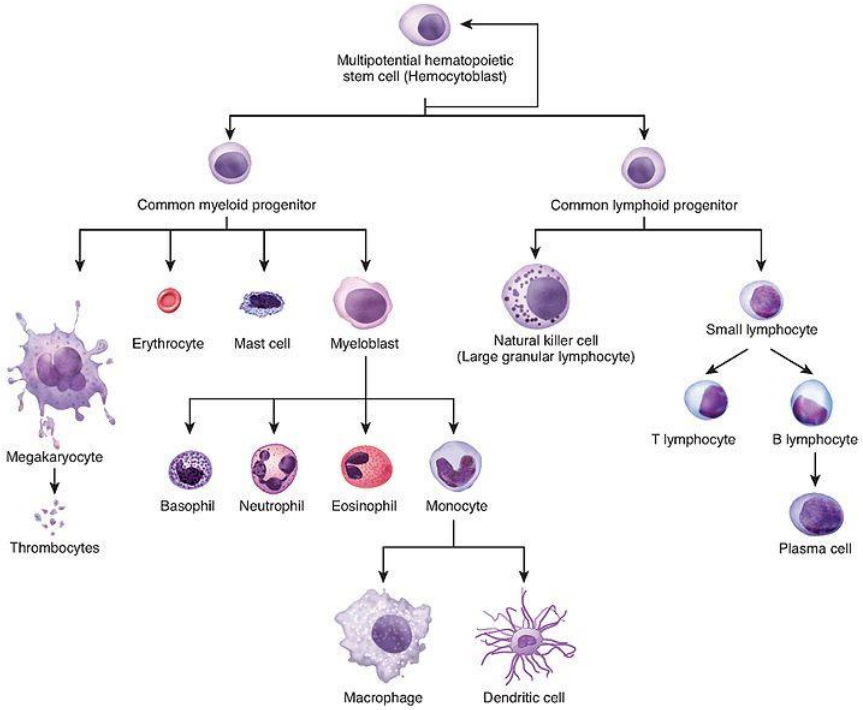
Deficiency in RBCs or in hemoglobin.

Symptoms of anemia:

Pallor, dizziness, fatigue & exertional dyspnea.

Degrees of anemia:

1) Mild: Hemoglobin concentration = 10-12 g / 100 ml.
2) Moderate: Hemoglobin concentration = 5-10 g / 100 ml.
3) Severe: Hemoglobin concentration < 5 g / 100 ml.



Causes of Anemia

1) Anemia due to a deficiency of RBCs formation factors
   a- Iron deficiency anemia.
   b- Vit B12 deficiency anemia.
   c- Folic acid deficiency anemia.
   d- Erythropoietin deficiency anemia.

Note:

Vit B6 deficiency is rare and causes anemia similar to Fe-deficiency microcytic anemia. Vit B6 is important for amino-levulinic acid “ALA” synthase which makes heme. Its deficiency is one of the causes of “sideroblastic anemia” in which iron is not incorporated to synthesize “heme” inside erythroblasts, and so iron accumulates forming a ring around the nucleus.

2) Hemolytic anemia

Due to some factors that destroy RBCs like:

* Some congenital disorders. (G6PD deficiency)
* Some drugs. (e.g. antimalarials, sulfonamides in G6PD-deficienct kids)
* Some diseases.
  - malaria.
  - thalassemia. (= Mediterranean anemia; an autoimmune disease)
  - sickle cell anemia: crescent RBCs that block small vessels & burst quickly.

3) Aplastic anemia

Due to some factors that inhibit the bone marrow like:

* radiations.
* some drugs. (e.g. chloramphenicol, anticancer drugs…...etc)
* some diseases. (e.g. chronic bone infections, malignant tumors)

4) Blood loss:

* bleeding. (accidents, cancer, peptic ulcer, heavy menstruation....)

Note: Microcytic vs macrocytic vs normocytic anemia:

* In anemia, the size of RBC could be small (microcytic), normal (normocytic), or big (macrocytic). The “Mean Corpuscular (or cell) Volume” MCV is the measure and is calculated (by an equation or by automated equipment) as part of a complete blood count. It allows us to classify anemia. The normal is 80-100 femtoliters or cubic microns (femotoliter = 10^{-15} L).

✍ Hemolytic, aplastic anemia or blood loss ⇨ normo-cytic anemia.

✍ ↓ Iron & thalessemia ⇨ micro-cytic anemia (MCV can reach 60-70 fL).

✍ ↓ vit B_{12} or folic acid ⇨ macro-cytic (megaloblastic; up to 150 fL)

* To determine whether the cause of macrocytic anemia is lack of folic acid or lack of vit B_{12} :

1) Measure serum levels of the 2 vitamins.
2) Vit. B_{12} deficiency is accompanied by neurological abnormalities. (e.g. numbness, pain, ataxia, incoordination)

* If anemia is caused by ↓ vit B12, giving folic acid will mask the symptoms of anemia but will not treat the neurological symptoms. So we need to give both vit B12 and folic acid if the exact cause of macrocytic acid is not determined.

Drugs used in Anemia

1) Iron (oral usually)

Iron deficiency is the most common cause of chronic anemia.

Significance of Iron:

It is the central atom in “heme” and in “hemoglobin”.

(heme + globin → hemoglobin)

♠ Our body needs 10-15 mg of iron daily from which it absorbs only 0.5-1 mg.

♠ Iron requirements increase in children, pregnant women, nursing mothers, heavy menstruation women.

Sources:

A) Animal sources (heme iron)

- In red meat & liver (easily absorbed).

(because “heme iron” in hemoglobin & myoglobin of meat can be absorbed intact without having to be dissociated into elemental iron)

B) Plant sources (Non-heme iron)

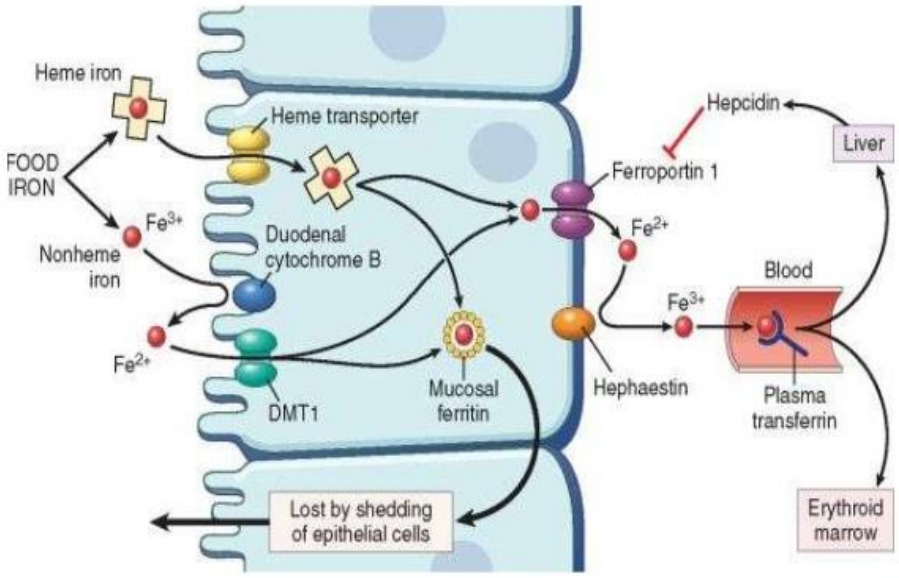
- In vegetables & grains (not easily absorbed).

(because iron is often tightly bound to organic compounds)

Factors altering iron absorption

- Factors that increase iron absorption:
  * Acidic medium.
    (ascorbic acid, citric acid & gastric HCl convert Fe^{3+} into absorbable Fe^{2+})

- Factors that decrease iron absorption:
  * Antacids.
  * Chelating agents: tannins, phytates, tetracyclines



DUODENAL EPITHELIAL CELL UPTAKE OF HEME AND NONHEME IRON.

Pharmacokinetics

❶ Only 10% of iron is actively absorbed mainly from duodenum.

❷ Fe^{3+} from food is converted into Fe^{2+} in the gut to be absorbed (by duodenal cytochrome B; heme iron is easily absorbed)

❸ Inside duodenum epithelial cells:

➥ "Apoferritin" carries Fe^{2+} forming "ferritin" then "ferroportin 1" helps Fe^{2+} to pass to blood.

❹ In the blood transferrin carries iron to reach:

➥ bone marrow (to synthesize hemoglobin) or
➥ Hepatocytes (to be stored as ferritin)
➥ muscles. (to be stored as myoglobin)

* "Fe bound to apoferritin" in tissues or gut mucosa is called ferritin (Note that aggregations of ferritin + proteins are called hemosiderin)

Indications:

The only indication of iron is “iron deficiency anemia”.

Preparations:

1) Oral iron

Ferrous iron (Fe^{2+}) is the most efficiently absorbed.

So only ferrous salts should be used like:

- ferrous sulfate, ferrous gluconate or ferrous fumarate.
- Duration: 3-6 mths. (1×3 after meals to prevent GIT side effects)

2) Parenteral iron (rarely used; slow i.v. or infusion)

Iron dextran is used only for patients unable to absorb oral iron.

Iron dextran is rarely used because:

- If i.v. ⇨ may cause anaphylactic shock.
- If i.m. ⇨ painful, cause brown coloring

Ferric gluconate, ferric carboxymaltose & iron sucrose (Venofer®) are newer & cause less anaphylaxis than iron dextran.

☠ Acute toxicity:

Although adults tolerate large doses of iron, 10 tablets of iron can be lethal in young children.

Symptoms:

👍 necrotizing gastro-enteritis, vomiting & bloody diarrhea.

✌ shock, lethargy & dyspnea.

Treatment:

✈ Gastric wash. (↓ absorption)

✈ Deferoxamine i.m. or i.v. (binds Fe^{3+} → ↑ excretion)

Contra-indication:

💣 In hemolytic anemia.

Release of Fe from destroyed cells plus oral Fe ⇨ deposition of iron in tissues ⇨ hemosiderosis ⇨ failure of organs & death.

2) Vitamin B12 (cobalamins)

Vit. B12 acts as an intermediate in 2 essential reactions:

❶ ↑ isomerization of "methyl-malonyl-CoA" to "succinyl CoA".
Succinyl CoA helps in the formation of myelin sheath of nerves.
So ↓ vit. B12 ⇨ ↓ succinyl CoA ⇨ neurological problems.

❷ Folic acid activation.
So ↓ vit. B12 ⇨ ↓ folic acid activation ⇨ ↓ DNA synthesis ⇨ ↓ cell division (esp. RBCs)

☑ The active form of vit. B12 in the body is:
→ methyl-cobalamin & deoxy-adenosyl-cobalamin.
☑ Vit. B12 is stored in the liver

Sources:
Animal products like liver, meat, eggs, milk & dairy products.
(synthesized in these products by bacteria)

Deficiency:
leads to ➢ anemia.
➢ neurological abnormalities.
(numbness, progressive spasticity & ataxia)

Causes of Vit. B12 Deficiency anemia:
1) ↓ diet. (rare)
May be seen in strict vegans after years of not ingesting meat, eggs or diary products

2) ↓ absorption of vit. B12 due to:
➢ ↓ intrinsic factor.
(due to pernicious anemia, partial or total gastrectomy...)
➢ mal-function of the vit. B12 transport system.
(mal-absorption syndrome, inflammatory bowel disease, ilium resection)

Preparations:

☑ Parenteral (i.m.) as cyano-cobalamin or hydroxo-cobalamin.

Hydroxo-cobalamine is better because it is strongly bound to plasma proteins ⇨ longer half life.

☑ Oral (vit. B12 + intrinsic factor)

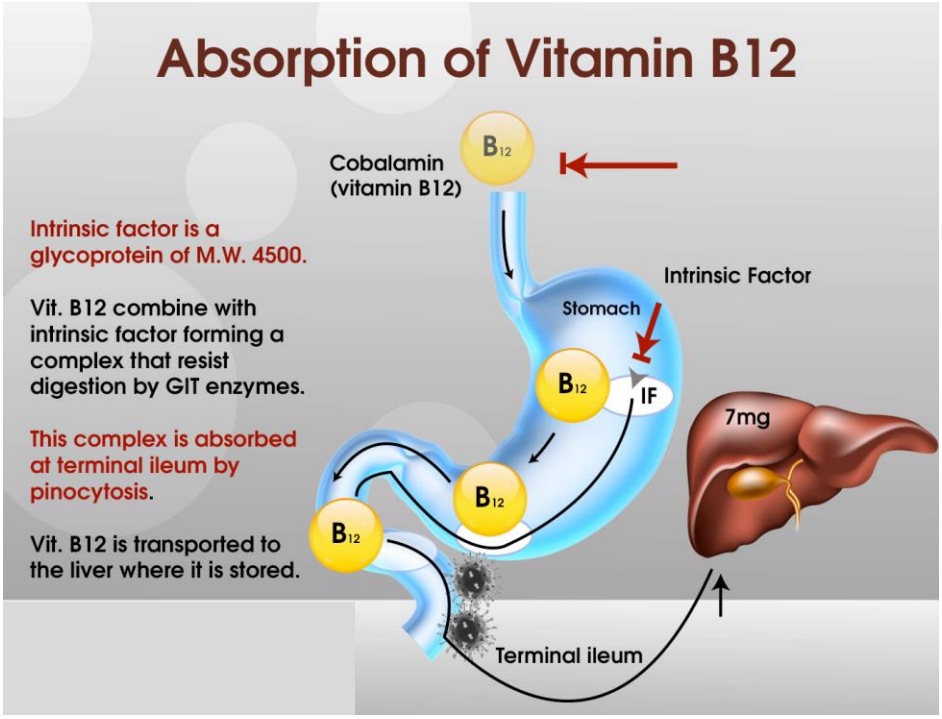
For pernicious anemia patients who cannot tolerate injections

Dose:

- Initially: 100-1000 µg / day for 1-2 weeks.
  (To replenish body stores)
- Maintenance: 100-1000 µg / month for life. (mostly)

**** Pernicious anemia (autoimmune)**:*

Atrophy in the stomach ⇨ no ability to secrete the Intrinsic Factor which helps to absorb vit. B12 (by a highly specific transport system in the distal ileum)


Absorption of Vitamin B12
Cobalamin (vitamin B12)
B12
Intrinsic factor is a glycoprotein of M.W. 4500.
Vit. B12 combine with intrinsic factor forming a complex that resist digestion by GIT enzymes.
This complex is absorbed at terminal ileum by pinocytosis.
Vit. B12 is transported to the liver where it is stored.
Intrinsic Factor
Stomach
IF
7mg
Terminal ileum

3) Folic acid (Vit B9; pteroyl glutamic acid; oral)

Significance:

Cell division.

(Folic acid is a methyl-donor required for the synthesis of purines & DNA.
DNA is required for all new-forming cells such as RBCs!)

Sources:

Liver, meat, green vegetables.

- Primarily as N^5-methyl-tetrahydro-folate but other folates also exist.
- In cells, N^5-methyl-tetrahydro-folate is converted into "tetrahydro-folate" (this requires vit. B12)
- Folic acid is a synthetic form in drugs and fortified food and is better absorbed

Causes of folic acid deficiency:

1) ↓ dietary intake.

2) Some drugs. (methotrexate, trimethoprim, pyrimethamine, phenytoin)

Consequences of folic acid deficiency:

1) Anemia.

↓ cell division in rapidly-dividing cells in the bone marrow.

2) In pregnancy ➡ congenital malformation in newborns.

↓ cell division in rapidly-dividing cells in all fetus cells.

(neural tube defects e.g. spina bifida & anencephaly)

Preparations:

oral.

Side effects of folic acid:

Hyper-uricemia.

(↑ folic acid ⇨ ↑ purines synthesis which are metabolized to uric acid)

* Folinic acid (leucoverin) is an active form of folic acid:

- Specifically indicated for counteracting toxicity of high dose methotrexate. (it is more expensive than folic acid)

Notes

- Giving folic acid in case of vit. B12 deficiency anemia:
  - will treat the anemia.
  - will NOT treat the neurological symptoms.

- Folic acid:

= Ptero-glutamic acid = pteridine + PABA + glutamic acid.

- Hematocrit:

The volume of RBCs in blood expressed as a fraction of total blood volume. Hematocrit is also used to determine anemia.

4) Hematopoietic growth factors

Erythropoietin

Hormone secreted from the kidney to stimulate RBCs formation.

Factors increasing erythropoietin secretion:

Tissue hypoxia. (high altitudes...)

Indications:

Anemia due to chronic renal failure.

Anemia resulting from anticancer drugs.

Preparations:

Vials. (i.v. or s.c. 3 times / week)

- Epoetin alfa = recombinant erythropoietin.
- Darbepoetin alfa = glycosylated erythropoietin.
  (2-3 times longer t½)

Side effects: ↑ BP & thrombosis

Notes:

♫ Hemoglobin is a protein inside red blood cells which:
1) Gives blood its red color.
2) Carries O2 to all parts of the body.

♫ Normal number of RBCs = 5,000,000 / mm^3.
Normal number of WBCs = 5000 / mm^3.
Normal number of platelets = 200,000 - 400,000 / mm^3.

♫ Thalassemia (Mediterranean anemia):
A hereditary disease widespread in the Mediterranean countries, Asia & Africa.
If hemoglobin is abnormal ⇨ RBCS are smaller & cannot function normally.
* If inherited from 2 parents ⇨ severe ⇨ major thalassemia
→ treated by repeated blood transfusions or bone marrow transplantation.
* If inherited from 1 parent ⇨ symptom-free.

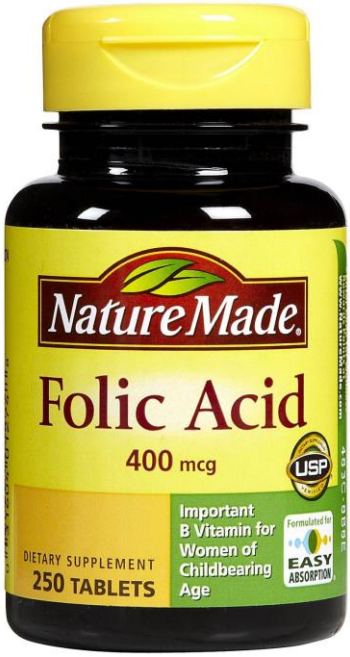
♫ Hormones which stimulate differentiation of stem cells into blood cells are:
1) Erythro-poietin ⇨ ↑ RBCs production from stem cells.
2) Thrombo-poietin & interleukin-11 ⇨ ↑ Platelet production.
3) Granulocyte-monocyte colony stimulating factor (GM-CSF= CSF2) & granulocyte colony stimulating factor (G-CSF = CSF3) ⇨ ↑ WBCs

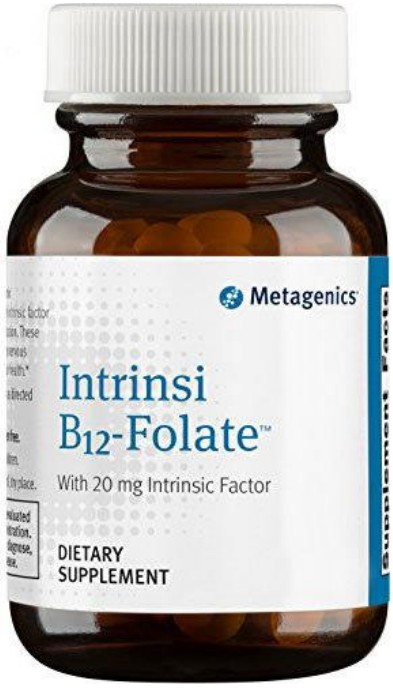
♫ Sargramostim is a recombinant GM-CSF
Filgrastim is a recombinant G-CSF

♫ In case of neutropenia (low neutrophils), Filgrastim (recombinant G-CSF) can be used parenterally (i.v. or s.c.). It can be used to treat neutropenia following chemotherapy, radiation poisoning, bone marrow transplantation or AIDS. Biosimilars are also available.

♫ Endogenous G-CSF is produced by monocytes, fibroblasts, & endothelial cells and GM-CSF is produced by macrophages, fibroblasts & endothelial cells.

tot'héma®
50 mg/ 1,33 mg/ 0,70 mg/ 10 ml
Oral solution
Iron / Manganese / Copper
Oral use


Nature Made
Folic Acid
400 mcg
USP
DIETARY SUPPLEMENT
250 TABLETS
Important B Vitamin for Women of Childbearing Age
Formulated for
EASY ABSORPTION


Metagenics
Intrinsi
B12-Folate™
With 20 mg Intrinsic Factor
DIETARY
SUPPLEMENT

Chapter 8

Drugs for Hyperlipidemia

= Anti-hyper-lipidemic Drugs

= Lipid Lowering Drugs

Hyperlipidemia

Definition:

A state in which there are excess lipids in blood leading to:

→ lipid accumulation inside walls of arteries

→ atherosclerosis (which restricts blood flow)

→ serious complications (e.g. ↑ BP, myocardial infarction or stroke)

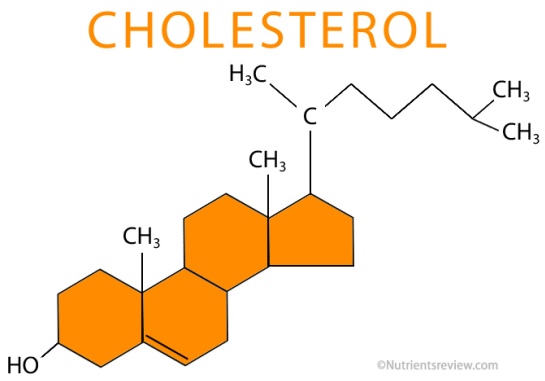
There are 3 types of lipids in blood:

- Cholesterol
- Triglycerides
- Phospholipids

1) Cholesterol:

Important for the body to make:

- bile acids
- steroid hormones
- minor component in the cytoplasmic membrane of all cells



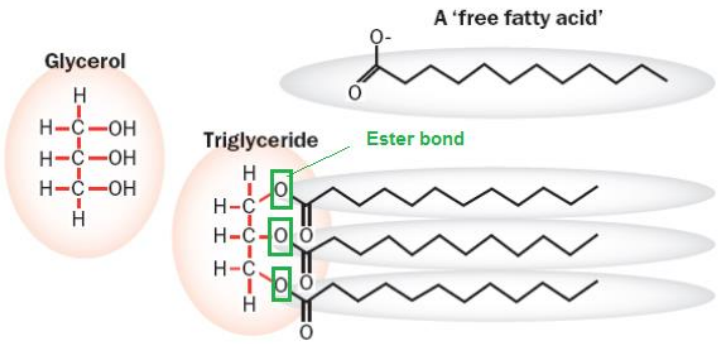
2) Triglycerides:

- Consists of a glycerol attached to 3 chains of fatty acids.

Function:

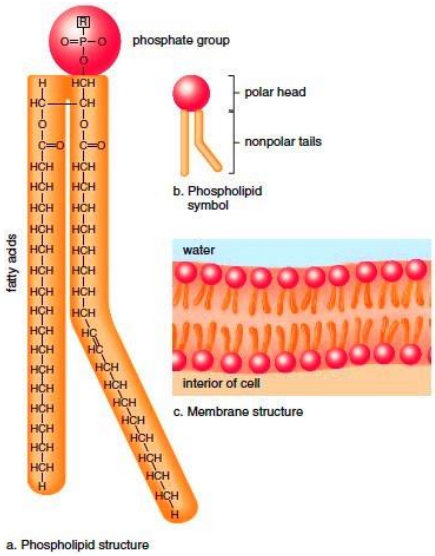
A main source for energy production

(stored under the skin in many parts of the body)



3) Phospholipids:

- The main component of all cell membranes.
- Also act as emulsifiers to help transport cholesterol in blood



Lipoproteins

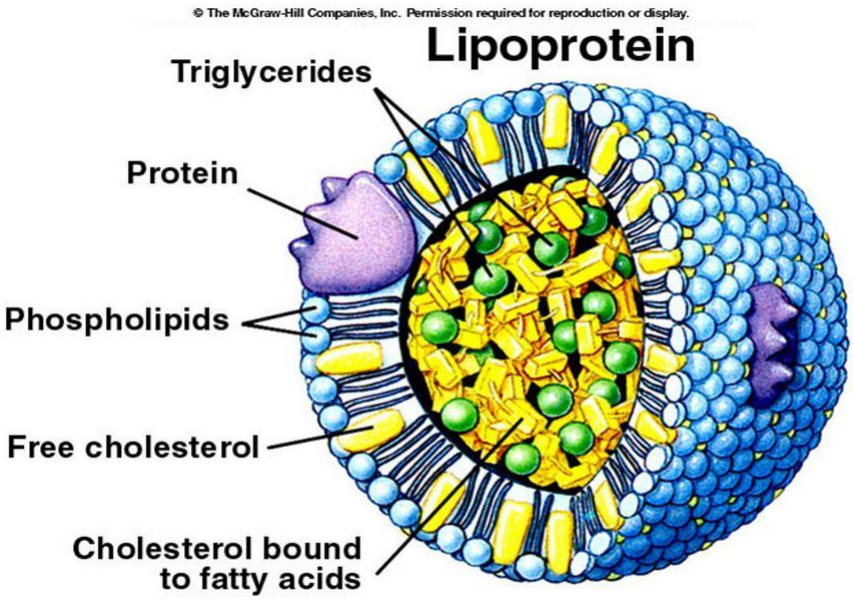
Lipids are insoluble in blood, so they need to be transported inside a capsule-like structure called lipoprotein.

These lipoproteins are composed of:

1) INNER hydrophobic core (cholesterol & triglycerides)
2) OUTER hydrophobic shell (apo-lipoproteins & phospholipids)

The apo-lipoproteins:

1) Act as ligands that can bind to lipoprotein receptors
2) Control enzymes of lipoprotein metabolism



Now, depending on composition (lipid and apo-lipoprotein composition) and thus density, lipoproteins are classified into 4 types:

1) Chylomicrons

2) VLDL (Very Low Density Lipoproteins)

3) LDL (Low Density Lipoproteins)

4) HDL (High Density Lipoproteins)

* Total cholesterol levels ≤ 200 mg/dL normally.
* Triglycerides < 150 mg/dL normally.
  (Borderline high:150-199. High: 200 to 499 mg/dL)

1) Chylomicrons:

- Made in the intestines from dietary lipids and transferred to liver
- Contain:
  1) mainly triglycerides
  2) very little cholesterol

2) VLDL:

- Made in the liver
- Contains:
  1) triglycerides
  2) little cholesterol (but more than in chylomicrons)

Function of Chylomicrons & VLDL:

→ To transfer (energy-rich) triglycerides to cells in the body.

(while chylomicrons & VLDL circulate in blood, they bind to receptors then "lipoprotein lipases" in tissue capillaries break down triglycerides in chylomicrons & VLDLs to release free fatty acids that are taken up by tissues)

3) LDLs:

As VLDL release free fatty acid into tissues, they become smaller and relatively richer in cholesterol (now called LDL)

Function of LDL:

To transfer cholesterol into cells to help in making:

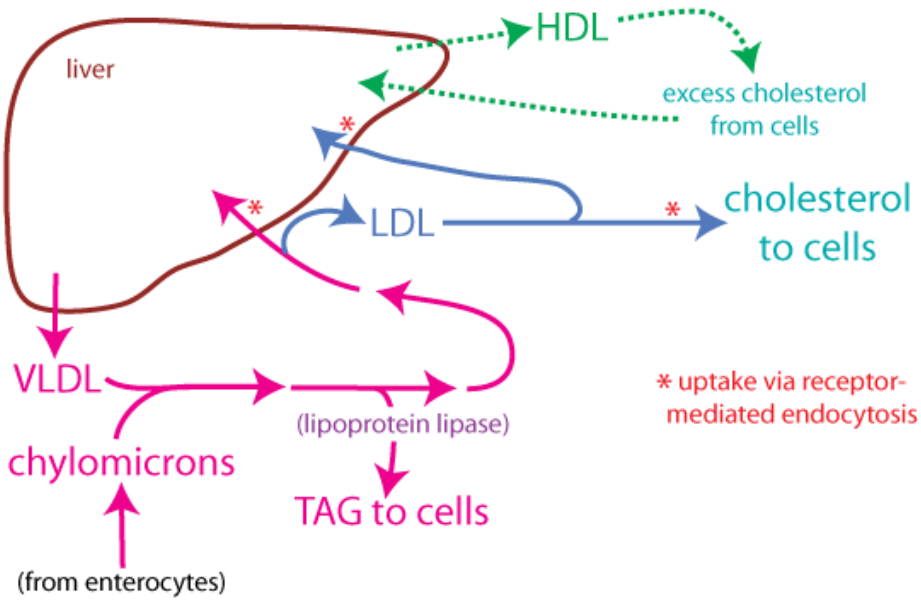
- cell membranes.
- steroid hormones.
- bile acids in the liver (50% is taken up by liver)

(but excess LDL can accumulate in the walls of arteries → atherosclerosis)

4) HDL:

Excess cholesterol in tissues and vessel walls is taken up by HDL (acts as a vacuum cleaner) which transfer it into the liver.

- HDL is originally made in the liver and small intestines.
- HDL contains:
  - mainly proteins
  - little lipids



Q) Where is the problem?

When there is a lot of cholesterol in the liver (e.g. from food),

→ LDL receptors will be downregulated.

→ LDL levels in blood will increase

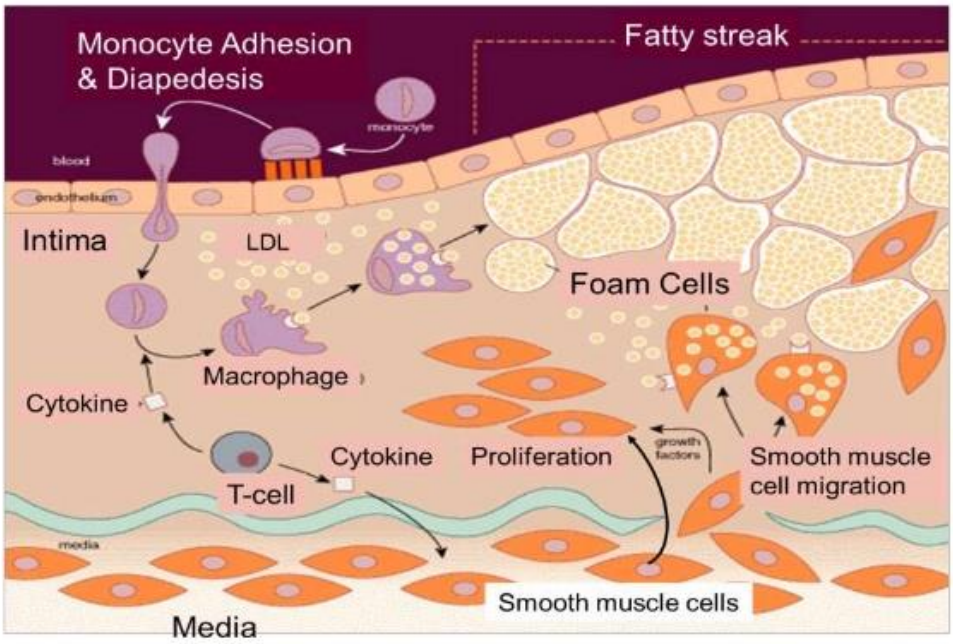
→ LDL and other lipids will accumulates inside the artery wall

→ atherosclerosis.

This is why LDL (which transfers cholesterol) is called “bad cholesterol”

HDL, on the other hand, takes up excess cholesterol to the liver (so called “good cholesterol”)

So high LDL and low HDL are factors in causing atherosclerosis!



How atherosclerosis is formed

Lipid Lowering Drugs

1) HMG-CoA reductase inhibitors (statins)
2) Fibric acid derivatives (fibrates)
3) Niacin (nicotinic acid; vit B3)
4) Bile acid sequestrants
5) Cholesterol absorption inhibitor (Ezetemibe “Zetia®”)

Notes:
- Non-drug therapies should be tried for at least 6 months before lipid-lowering drugs are used
- Total cholesterol is the sum of LDL-C, VLDL-C, and HDL-C.
- Risk of atherogenicity:
  LDL > VLDL > chylomicrons >>>> HDL
- So reduction of LDL-C is the primary goal.

1) "HMG-CoA reductase" inhibitors (statins)

* Inside hepatocytes, cholesterol is synthesized:

HMG-CoA → mevalonic acid → → → → → cholesterol

(Note that the 1st step above is the "rate-limiting step" in cholesterol synthesis and is mediated by "HMG-CoA reductase")

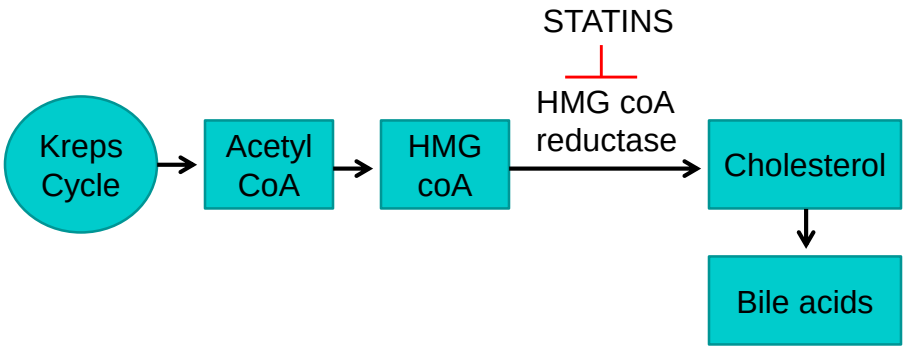
MOA:

1) ↓ HMG-CoA reductase → ↓ cholesterol synthesis, This leads to:

- hepatocytes compensate by upregulation of LDL receptors to take up LDL from blood → ↓ cholesterol in blood

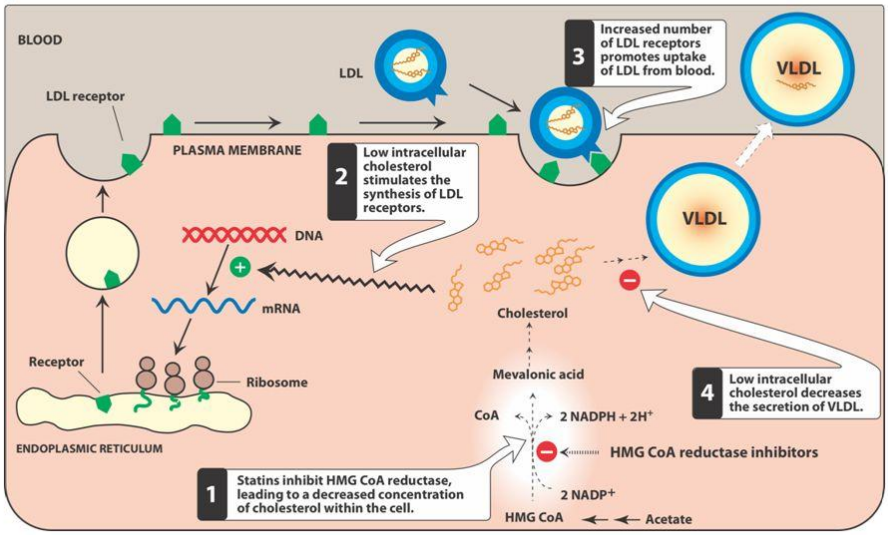
- Also, ↓ cholesterol production in liver leads to → ↓ VLDL production → ↓ triglycerides & LDL in blood.

2) Statins also increase HDL by unknown mechanisms



Statins: Mechanism of Action

HMG CoA Reductase Inhibitors (statins)



Harvey RA. *Lippincott's Illustrated Reviews: Pharmacology*. 5th ed. Baltimore, MD: Lippincott, Williams & Wilkins; 2012.

Drugs:

- atorvastatin (Lipitor®)
- rosuvastatin (Crestor®)
- pitavastatin (Livalo®)

} most potent

- simvastatin (Zocor®)
- pravastatin (Pravachol®)

} potent

- lovastatin (Mevacor®) (1st to be synthesized)
- fluvastatin (Lescol®)

} Less potent

S.E:

1) Hepatotoxicity (reversible; switch to another statin)

2) Myalgia (10-20%; switching helps) and rhabdomyolysis (rare)

3) Hyperglycemia

☺ Advantages of statins:

- ☺ Best in reducing LDL (1st choice)
- ☺ ↓ atherosclerosis & clots in the following 5 yrs by 30%
- ☺ ↓ heart attacks
- → among the top sellers in the world

Notes:

* Statins cause hepatotoxicity because they stop synthesis of cholesterol and thus VLDL. So fats will not easily leave the liver and then may damage it.

* Statins are thought to lower coenzyme Q10 (coQ10) production which is important for muscles → myositis and possibly rhabdomyolysis. Chunks for proteins can block nephrons and lead to acute renal failure and possibly death.

Who should take statins?

1) LDL-C > 190 mg/dL
2) Diabetes
3) Had a heart disease or stroke
4) Family history of cardiovascular disease
5) Increasing age
6) Obesity

Notes:

- Statins are usually taken at night. Why?
  1) Most cholesterol synthesis occurs at night
  2) If myalgia or fatigue occurs, it is better to have them at night

  (some statins like atorvastatin can be taken anytime of the day)

How to deal with side effects of statins?
1) Switch to another statin

2) Decrease frequency (3 days/week)

Notes:
* Fibrates + statins → ↑↑ hepatotoxicity & muscle pain

* Bile acid resins + statins → ↓ absorption of statins
(take statins 1 hr before or 4 hrs after taking the resins)

* HMG-CoA = 3-Hydroxy3-Methyl-Glutaryl coenzyme A

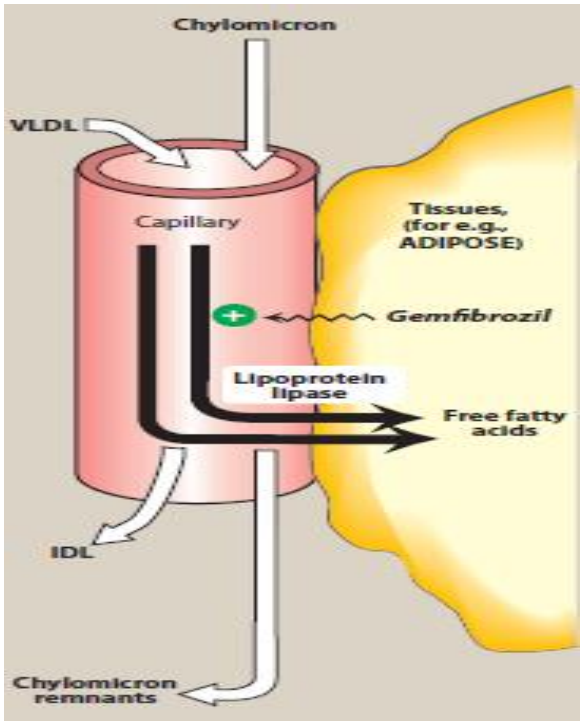
* Simvastatin is the only OTC statin in Britain
(in small doses of 10 mg).

2) Fibrates (fibric acid derivatives)

Fenofibrate, Gemfibrozil, Clofibrate, bezafibrate
MOA:
↑ PPAR-α leading to:
1) ↑ "lipoprotein lipase" expression (in endothelial cells)
→ ↑ removal of triglycerides from blood into adipose tissue.
2) ↓ expression of ApoC-III in the liver (a component of VLDL)
3) ↑ expression of ApoA-I & -II (components of HDL)

SE:
1) GIT side effects
2) Hepatotoxicity
3) Myopathy & possibly rhabdomyolysis
4) ↑ HDL → ↑ cholesterol to the gall bladder → gall stones

MOA of fibrates



Lippincott 2015

Use:

Usually in combination with statins (usually not alone)

General notes:

- Fenofibrate is more effective than gemfibrozil in lowering triglyceride levels.
- Fibrates decrease the triglycerides & increase HDL by as much as 25%
- Main advantage of fibrates → best in lowering triglycerides

3) Niacin “Nicotinic acid; vit B3”

Site of action:

In the adipose tissue (not in the liver like statins)

MOA:

1) ↑ niacin receptors 1 & 2 → ↓ “lipase” in the adipose tissue
   → ↓ FFA release into blood
   → ↓ FFA uptake by liver
   → ↓ VLDL synthesis by liver
   → ↓ LDL levels
2) ↑ HDL by unknown mechanisms

SE: (vit B3)

1) Flushing (↑ PGs release; combine with Aspirin)
2) Gout & Hyper-uricemia (competes with uric acid on active secretion)
3) Hyperglycemia

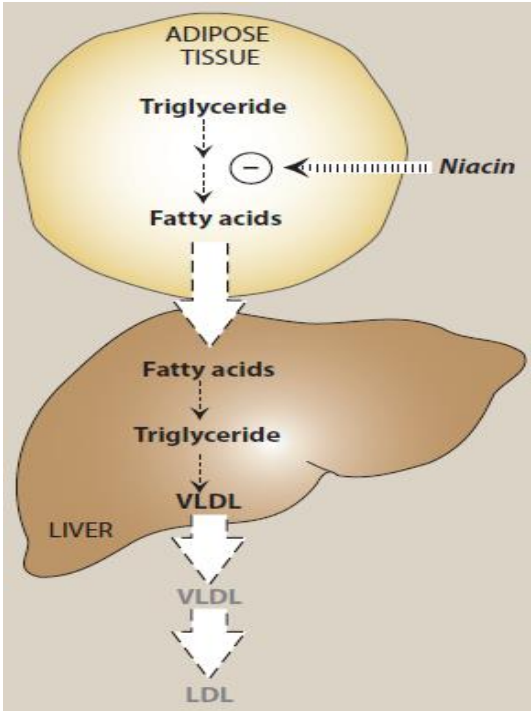
Notes on niacin:

* Advantages for niacin:
  - ☺ The best in increasing HDL
  - ☺ Effective
  - ☺ Cheap
  - ☺ Also ↓ triglycerides by 20% to 35%”

* Niacin (vit B3) deficiency leads to “Pellagra” which causes 3 Ds:
  - Dementia, Dermatitis, Diarrhea

* Lipid-lowering properties of niacin require much higher doses (grams) than when used as a vitamin
* Niacin also lowers triglycerides and LDL
* Niacin is often used with other lipid-lowering drugs

Niacin: MOA



Lippincott 2015

4) Bile acid sequestrants (2nd line drugs)

Bile acids are made in the liver and stored in the gall bladder and then secreted into the intestines to help digest and absorb lipids.

MOA:

Ion exchange resins.

→ Bind –vely charged bile acids in GIT

→ ↓ their absorption & ↑ excretion in feces

→ ↑ LDL receptors in the liver to take up cholesterol and make up more bile acids (to compensate for the excreted bile acids)

Drugs:

- Cholestyramine, Colesvelam, Colestipole (substitutes for statins)

SE: local (they are not absorbed)

1) They taste bad and cause GIT side effects
2) ↓ absorption of fat-soluble vitamins (K, E, D, A)
3) ↓ absorption of some drugs

5) Cholesterol absorption inhibitors

Normal cholesterol absorption:

Free cholesterol in GIT (from diet or from bile acids) binds a protein in the cell membrane of enterocytes called “NPC1L1” which triggers endocytosis of cholesterol via Clathrin AP2-mediated endocytosis

MOA of “Ezetimibe”:

↓ cholesterol absorption

(Inhibit NPC1L1 → ↓ Clathrin AP2-mediated absorption of cholesterol in the GIT → ↓ cholesterol reaches liver → ↑ LDL receptors in hepatocytes to compensate)

☺ Well-tolerated (may cause diarrhea)

☹ Modest effect

(so adjunct only or alternative in case of statin intolerance or resistance)

6) Omega3 fatty acids

- Polyunsaturated fatty acids found in fish and fish oil.
- Used mainly to lower triglycerides

MOA:

Inhibit synthesis of triglycerides & VLDL in the liver

Drugs:

* DHA = docosa-hexanoic acid
* EPA = eicosa-pentanoic acid
* Icosapent ethyl.

SE:

1) GIT side effects (fishy after-taste, nausea, pain, diarrhea)
2) In high doses → ↑ risk of bleeding

Use:

Adjunct to other drugs for individuals with significantly elevated triglycerides (≥ 500 mg/dL).

Notes:

- Fish oil capsules (EPA/DHA) can be used for supplementation, because it is difficult to consume enough omega-3 PUFAs from dietary sources alone.

- Icosapent ethyl is a prescription product that contains only EPA and, unlike other fish oil supplements, does not significantly raise LDL-C.

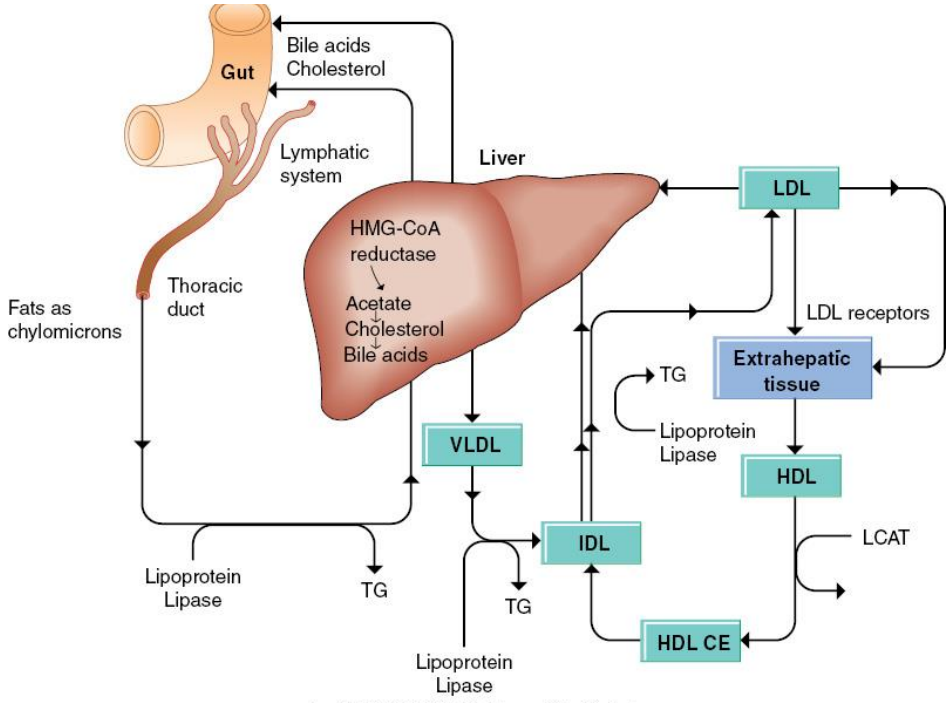
7) PCSK9 inhibitors

PCSK9 = enzyme binds to LDL receptors and trigger their degradation

MOA:
Antibodies that bind PCSK9 → inhibiting their effect

Drugs:
Evolcumab & Alirocumab (☹ only inj)

SE:
1) Injection site reactions
2) Flu-like symptoms
3) Neuro-cognitive problems



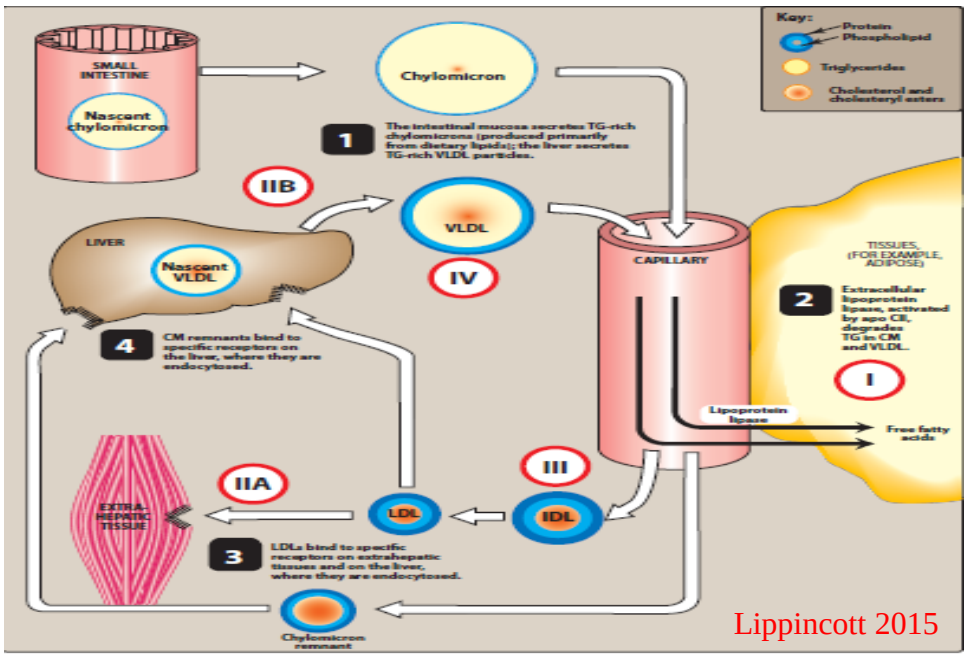


Figure 23.2
Metabolism of plasma lipoproteins and related genetic diseases. Roman numerals in the *white circles* refer to specific genetic types of hyperlipidemias summarized on the facing page. CM – chylomicron; TG – triglyceride; VLDL – very-low-density lipoprotein; LDL – low-density lipoprotein; IDL – intermediate-density lipoprotein; apo CII – apolipoprotein CII found in chylomicrons and VLDL. (Figure continues on next page.)

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIGLYCERIDES
HMG CoA reductase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	↑
Cholesterol absorption inhibitor	↓	↑	↓

Notes:

Q) Which drug is best in a patient with high LDL?

- Statins

Q) Which drug is best in a patient with high triglycerides?

- Fibrates

Q) Which drug is best in a patient with normal LDL but low HDL?

- Niacin

* Bile resins & Ezetemibe:

Adjunct in to statins in lowering LDL (weak)

* Omega-3 fatty acids:

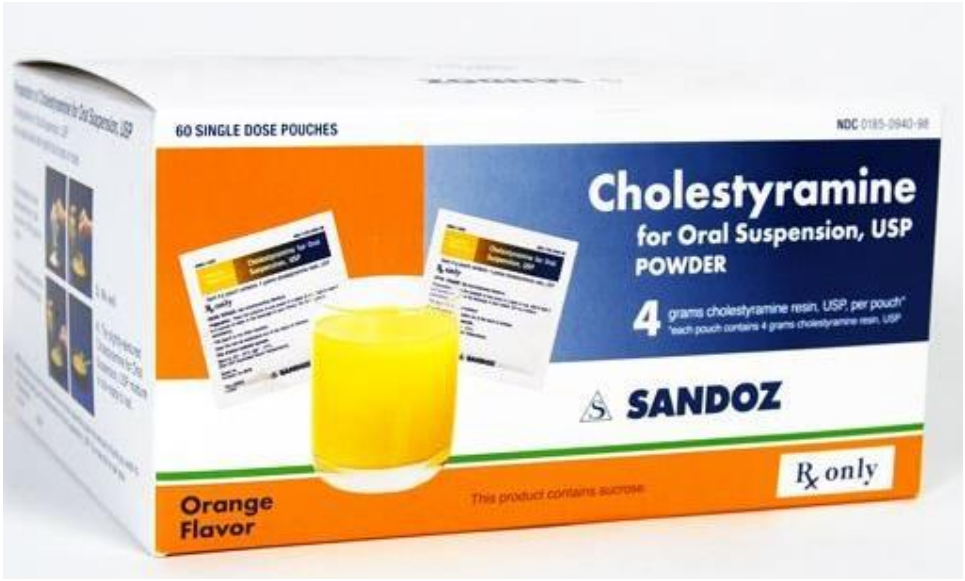
Adjunct in lowering triglycerides

Final notes:

- Patients on long-term therapy with lipid-lowering agents may need supplemental fat-soluble vitamins (A, D, K, E)
- Take drugs with meals to decrease GI upset
- Powder forms must be taken with a liquid (not dry)
- Small doses of aspirin or NSAIDs may be taken 30 min before niacin to minimize cutaneous flushing
- May take several weeks to show effectiveness
- No Drugs are safe in pregnancy (only diet & exercise are advised)
- Fibers in food act similar to bile acid sequestrants

50 Capsules
Clofibrate 500
Each capsule contains:
Clofibrate
500 mg
ZAHRAVI Pharm. Co. Tabriz - IRAN

Carlson
Niacin
50 mg
DIETARY SUPPLEMENT
Supports Cholesterol Metabolism*
300 Tablets


60 SINGLE DOSE POUCHES
Cholestyramine
for Oral Suspension, USP
POWDER
4 grams cholestyramine resin, USP, per pouch*
SANDOZ
Orange
Flavor
This product contains sucrose.
℞ only

EZETROL
30 tablets
EZETROL™ 10 mg
(ezetimibe)
MSD
Schering-Plough

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